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THE PHYSICAL WELFARE OF THE DIONNE QUINTUPLETS*

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THIS report of the physical welfare of the Dionne quintuplets covers the period of their first three years of life. It is presented with a hope that it may prove of interest and possibly of some value as well.

ENVIRONMENT

The children's home is situated across the road from the little farm where they were born. It was built in a rather barren field which showed irregular outcroppings of rock through an uneven ground. Since that time a great number of changes have taken place, so that at the present they live in a fully equipped, comfortable home, containing all modern conveniences. Their little estate is made up of about seven acres, and is surrounded by a heavy metal fence seven feet high and topped with barbed wire. The grounds within are prettily landscaped and contain many planted trees, a tiny garden, patches of lawn, and three buildings. At one side of the children's house, or main building, is the observation playground's structure. Here the general public may watch their play (through glass and a fine screen) from a protected corridor. By this means the

* Read at Symposium on Quintuplets at Toronto, October 30, 1937.

Fig. 1.—Present home.

observation periods are carried out with minimum noise for, and distraction of, the children. On the other side of the central building there is a comfortable duplex structure for housing certain members of the staff. There are a dozen occupied bird houses for the summer feathered visitors, distributed around within the enclosure. During the winter a feeding box is placed outside the nursery window to attract the birds. Electricity is brought out by a special line from the main highway and provides all the buildings with light, and certain equipment therein with carrying out the plans laid down for their early education. They are also responsible for the upkeep of a careful record system pertaining to their health and development. One of the nurses remains with the children each night. The three permanent policemen guard the children twenty-four hours of the day, supervise the observation periods for the general public, and help with many other duties about the various buildings. Further temporary help is needed during the summer, to look after the increased number of visitors.

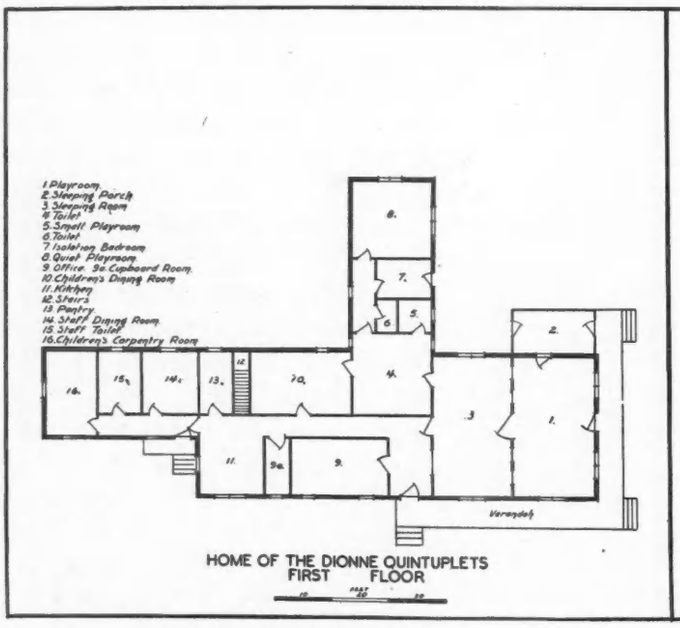

Fig. 2.—First floor of home.

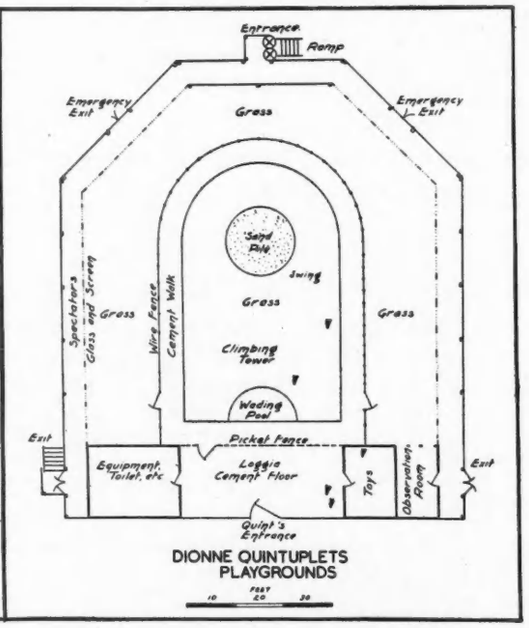

Fig. 3.—Observation playgrounds.

power and heat. This line also furnishes the Dionne home and their store. The water supply is obtained from a 68-foot drilled well about thirty feet north-east of the nursery. The sewage from the staff house and children's home is carried to a septic tank, forty yards north-west of the main house. From there the drainage continues to a well tiled field still farther away.

The permanent staff of the children's home consists of nine members, *i.e.*, two nurses and one teacher, three policemen, one housekeeper and two maids. One of the nurses has been specially trained in child-study and education. The policemen and the nurses live in the separate halves of the duplex building. The housekeeper and the maids have rooms in the main building. The three nurses are responsible for the care and training of the children and for

GUARDIANSHIP

The Dionne Quintuplet Guardianship Act which placed the children under the control of the Crown and appointed a guardianship for them until they reached the age of 18 was amended in April, 1937. This Amendment provided for the appointment of the Official Guardian of Ontario as one of the guardians, in place of the Minister of Welfare. There are three other guardians, the father, Judge Valin a retired jurist of North Bay, and Dr. A. R. Dafoe. The guardians, who meet once a month, have full control of all business affairs and other matters pertaining to the children's estate. They make contracts, pay expenses, and generally carry on with the duties associated with the children's care and welfare. The guardians serve without salary but employ a general business manager and a secretary-treasurer, and call

in legal advice to pass on all contracts and other business matters. All accounts are audited monthly by a firm of public accountants.

FINANCIAL ARRANGEMENTS

The income of the children is derived from contracts for motion and still pictures and for endorsements of products used in their home. Every contract must have the complete approval of their medical adviser and guardian and is subject to his interpretation of the possible effect on their physical and mental health. By an Order in Council of the Dominion Government, the use of the words Quins, Quints or Quintuplets and their French equivalents is forbidden for advertising purposes without the permission of the guardians.

The present invested financial holdings of the Guardianship held in trust for the Dionne quintuplets is approximately one-half million dollars. This amount includes the property value ($60,000) of their estate. The capital is invested in Government securities. The income from this capital is used to meet the expenses which amount to about $1,800 per month.

GENERAL CARE AND DAILY LIFE

Carefully observed regularity has been the essential principle followed in the general care of these children. They sleep, eat and play at regular hours, and nothing is allowed to interfere with this routine. For the first 18 months the babies slept 18 hours a day, which included the morning and afternoon periods. After that time one hour was taken off the morning, and at 21 months of age the morning sleeping period was omitted because the children were not sleeping throughout the night. Ever since then they have been sleeping 12 hours at night, and about 1½ hours in the afternoon. "Early to bed and early to rise" has been the rule in the nursery. In this, their third year, after arising and being dressed, they receive their orange juice and then their breakfast. Their play period follows breakfast, and during this time they are given interesting playthings, and occupations are suggested which allow them to use their little imaginations. The nurses are instructed to allow them as much freedom as possible with as little restraint as necessary. Before lunch they have music, songs and group-play for fifteen minutes, followed by a short rest on mats. In the afternoons they play outside again after their sleep. They are bathed just before supper, which is served at 6.00 p.m. They are then undressed and short simple stories are read to them, after which they say their prayers before being tucked into bed. The children are fortunate in having extensive wardrobes. Each one owns a complete ensemble which will suit the contingencies of any kind of weather, and when well they seldom miss their outside play-periods. Their house clothes are light in weight and colour throughout the year. The changing seasons and weather control the arrangements for their outside clothes. Cotton garments are always worn next to their bodies, and woollens are added as the weather becomes colder. They wear socks in the summer and stockings in the early spring, fall and winter. The children are encouraged to hang up their clothes and put away their shoes in their individual cupboards. They are also encouraged to help themselves in the act of dressing. Their teeth are brushed twice a day, and "pretend visits" to the dentist are carried out at intervals, so as to prevent any fear of the dental chair with its inevitable drill when the time comes for attention. There is a portable dental outfit in the home, and one of the nurses makes use of this, acting in the rôle of a dental surgeon. The daily routine also includes caring for their hair, nails and cleansing their hands and faces. Their reactions to these various procedures do not differ in any way from those of other children. Elimination training required considerable attention and patience, but these habits reached a stage of regularity when they were 2½ years old. The children are picked up every night at 9 o'clock, and bed-wetting has been a rare occurrence during the last year. The dining-room was especially designed for the children, and is decorated in white, with simple but attractive furniture. It contains three enamel-covered tables, six small chairs and a buffet. One of the tables is used for serving purposes, with proper containers to keep the food hot. One of the nurses takes her meals with the children and indirectly teaches them good table manners. Grace is said after they are seated, and then they take their dishes in turn for a helping of each course from the serving table. They are not allowed any dessert until they finish their main course, but, finishing that, they may have more than one helping.

After the meal is finished they take their turns in removing their dishes to the buffet and then return to their chairs from whence they are excused. Nourishment in the form of orange juice or acidophilus milk with biscuits is given halfway between meals, in the morning and afternoon.

PHYSICAL DEVELOPMENT

In spite of their prematurity at birth the children have rapidly progressed in their physical development, so that at the end of three years, with the exception of Marie, they have reached or exceeded the normal levels for weight and height. The accompanying charts show graphically this individual progress, together with the increase in a normal child for comparison.

Their general physical characteristics during their first three years of growth have appeared to be normal, with two exceptions. These exceptions were both associated with Marie. She was found to have a small hæmangioma at birth which kept growing fairly rapidly until it reached the size of a 50c. piece. The tumour was treated three times in one year, at six months' intervals, with radon tubes.* The total dosage was 750 millecuries of radium, filtered through 2 mm. of brass and 6 to 9 mm. of felt, and the growth has completely disappeared, leaving a faint purplish tinged area. Then again when she was 20 months old she began to walk with an unusual, slightly waddling gait. The possibility of a congenital dislocation at

* The radium emanations were applied by Drs. Howard and Edmund Kelly, Baltimore, Md.

DEVELOPMENT OF THE QUINTUPLETS

Average	*Weight* lb.	oz.	*Height* inches	*Head* inches	*Chest* inches	*Wrists* inches	*Ankles* inches
Quints at birth	2	11	13	10½	8½	1½	1 1/2
Quints at 3 years	30	8	31½	19½	21	4½	6 1/3
Normal 3 years	30	5	35½	19	19.8	–	–

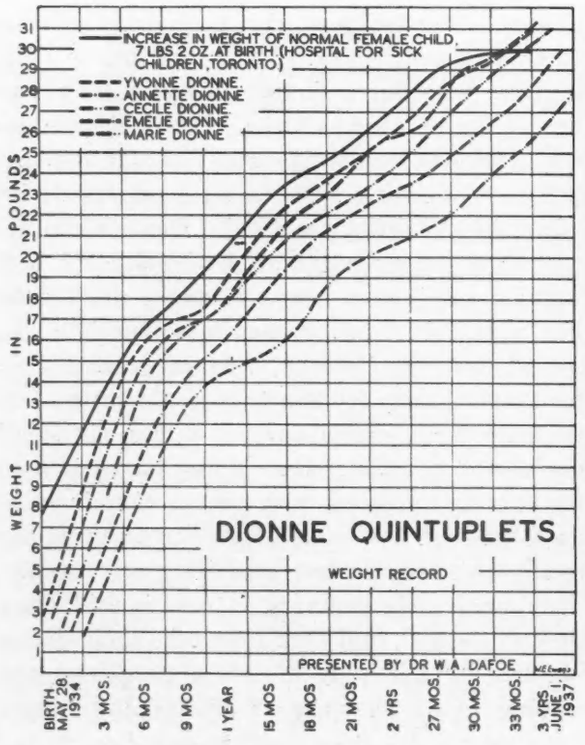

Chart 1.—Weight increase.

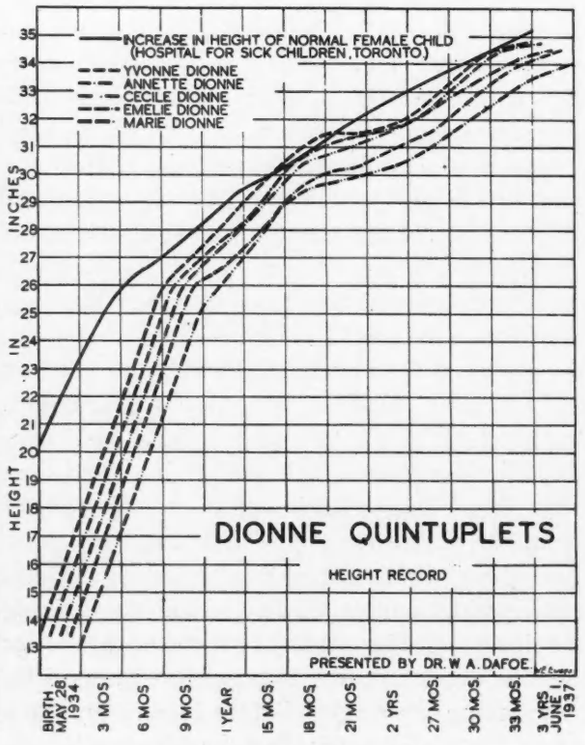

Chart 2.—Height increase.

the hip joints was considered. Dr. Rolph, of the Hospital for Sick Children, Toronto, kindly made an uncomfortable trip in mid-winter to take x-ray films for further information. At the same time films of the children's wrists were taken. The hip joints were found to be normal, and it was not long before Marie was toddling around like the others. The x-ray of the wrists showed a slight line of density at the metaphysis of the radius and ulna, which was probably the result of the anti-rachitic diet that the children received. The lower radial and the two carpal epiphyses were present and well developed. The age-appearance of these epiphyses varies according to authorities, but in these children they were found to be within the range of normal. The metacarpal epiphyses were present in an advanced stage of development that is usually found between the ages of 2 and 3.

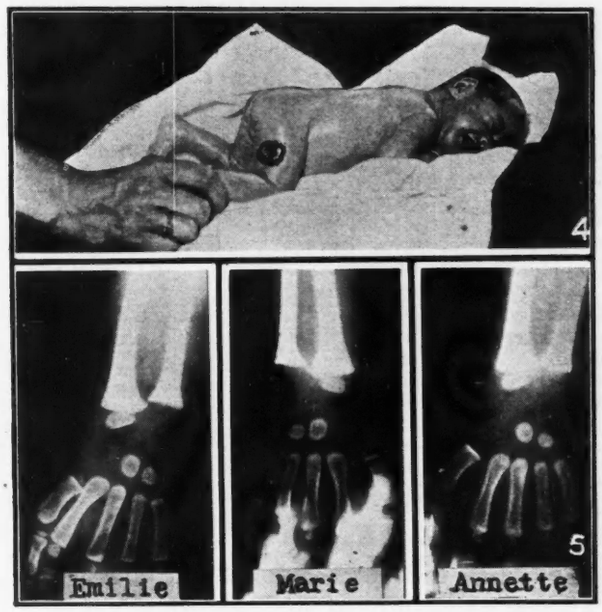

Fig. 4.—Hæmangioma of right thigh—Marie, aged 4 months.

Fig. 5.—X-ray of wrist showing radius and carpal and metacarpal epiphyses.

The eruption times of the deciduous dentition in the quintuplets have been definitely slower than normal. As a common finding, the first teeth in normal children are completely erupted by the end of 24 months (approximately). Here again it must be kept in mind that these children were premature and that there are no statistics available in a group of similar prematurity. Using Logan and Kronfeld's chart for normal human dentition, it is seen that the quintuplets' first teeth erupted from 3 to 7 months after the maximum time-limit given therein. The different types of teeth in both jaws made their appearance at approximately the same time, with the exception of Yvonne's

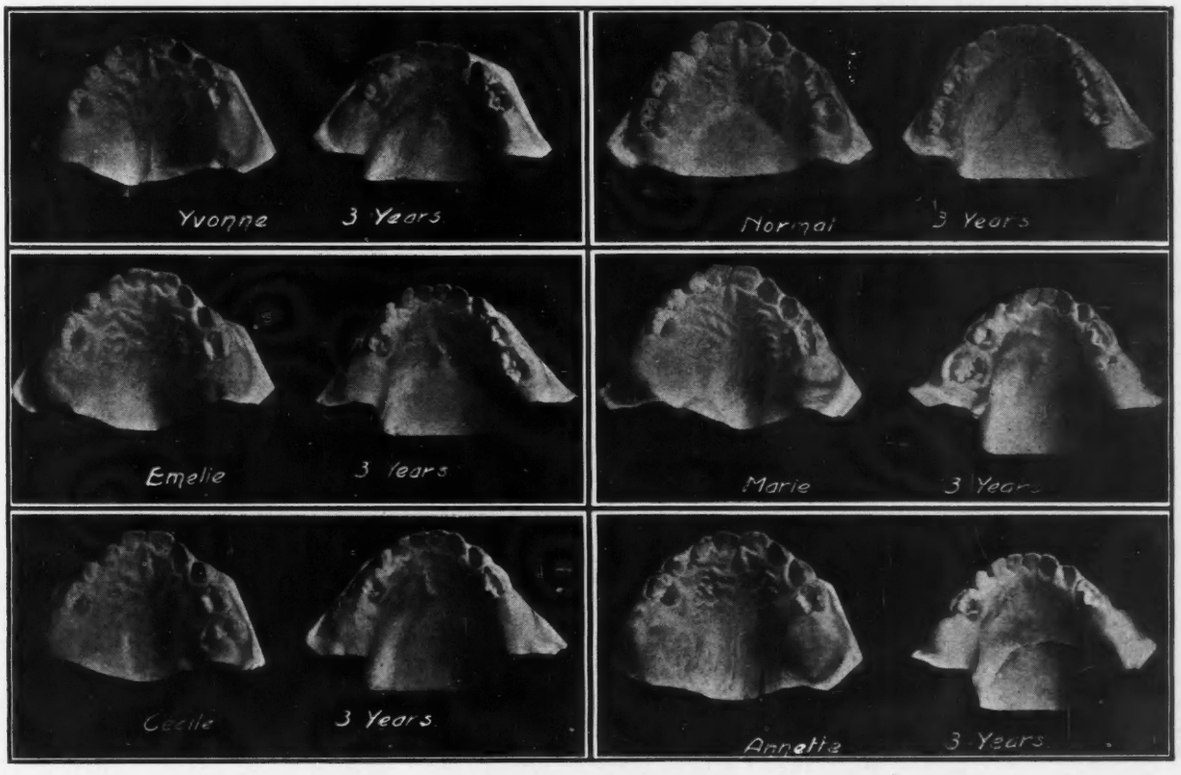

Fig. 6.—Dental casts.

right lower second molar (40 months). The dental casts show that there is tendency towards a narrowing of the arches, which has caused some crowding of the anterior teeth, and thus producing a rotation of the incisors. In Cecile's cast there is a protrusion of the upper central incisors which are not fully erupted, and this finding is suggestive of a thumb-sucking habit. This protrusion is present, but to a less extent, in Emelie's cast. The over-bite is normal with Emelie and Cecile, but somewhat excessive with the other three. The general alignment of the teeth in all the children is good, and there is no necessity of carrying out any corrective procedures. The only abnormality is found in Marie's double upper right molar. Dental caries is absent, and the teeth are hard in consistency and, with the exception of a greenish-brown stain found on Yvonne's, very white in colour.

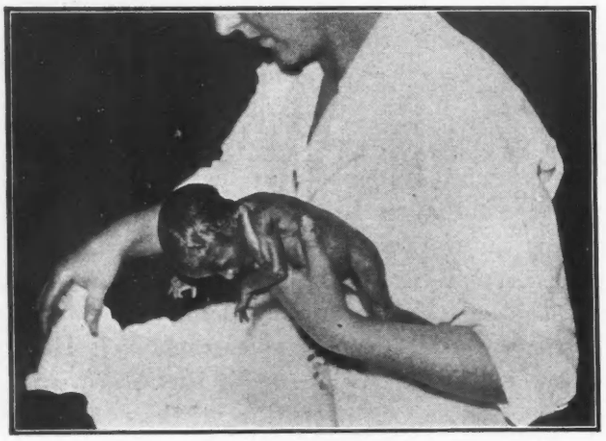

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Fig. 7.—Marie: two days old.

ERUPTION OF DECIDUOUS DENTITION
AGE IN MONTHS

	ANNETTE	EMELIE	CECILE	YVONNE	MARIE	QUINT'S APP. AVERAGE ERUPTION.	MAXIMUM NORMAL ERUPTION.*	ANNETTE	EMELIE	CECILE	YVONNE	MARIE	QUINT'S APP AVERAGE ERUPTION.	MAXIMUM NORMAL ERUPTION.*
CENTRAL INCISOR	13	14	13	12	14	13	8	12	14	13	12	13	13	8
LATERAL INCISOR	16	18	15	17	15	16	10	15	16	14	16	16	15	10
CUSPID	25	27	26	24	24	25	20	26	27	25	26	26	26	20
FIRST MOLAR	20	21	21	20	20	20	16	19	19	19	20	19	19	16
SECOND MOLAR	36	36	36	38	37	36	30	37	38	35	38	36	36	30
	RIGHT UPPER							LEFT UPPER						
	RIGHT LOWER							LEFT LOWER						
CENTRAL INCISOR	14	15	11	14	13	13	8	11	15	12	15	15	14	8
LATERAL INCISOR	16	17	14	17	15	16	10	16	16	15	16	16	16	10
CUSPID	23	25	23	22	23	23	20	23	24	23	24	23	23	20
FIRST MOLAR	18	20	19	30	18	21	16	20	18	19	19	18	19	16
SECOND MOLAR	37	34	37	?	36	?	30	38	37	36	39	35	37	30

?-ERUPTION NOT COMPLETED SEPT 26-40 MONTHS
*-DECIDUOUS DENTITION. (LOGAN AND KRONFELD)

Table I.

NUTRITION

Tables II, III and IV show the details of the children's diet throughout their three years of life. On the whole it has consisted of the five principal foods containing the growth, fuel, repair and roughage elements, together with added vitamines. The various foods were carefully chosen, slowly increased to meet the re-

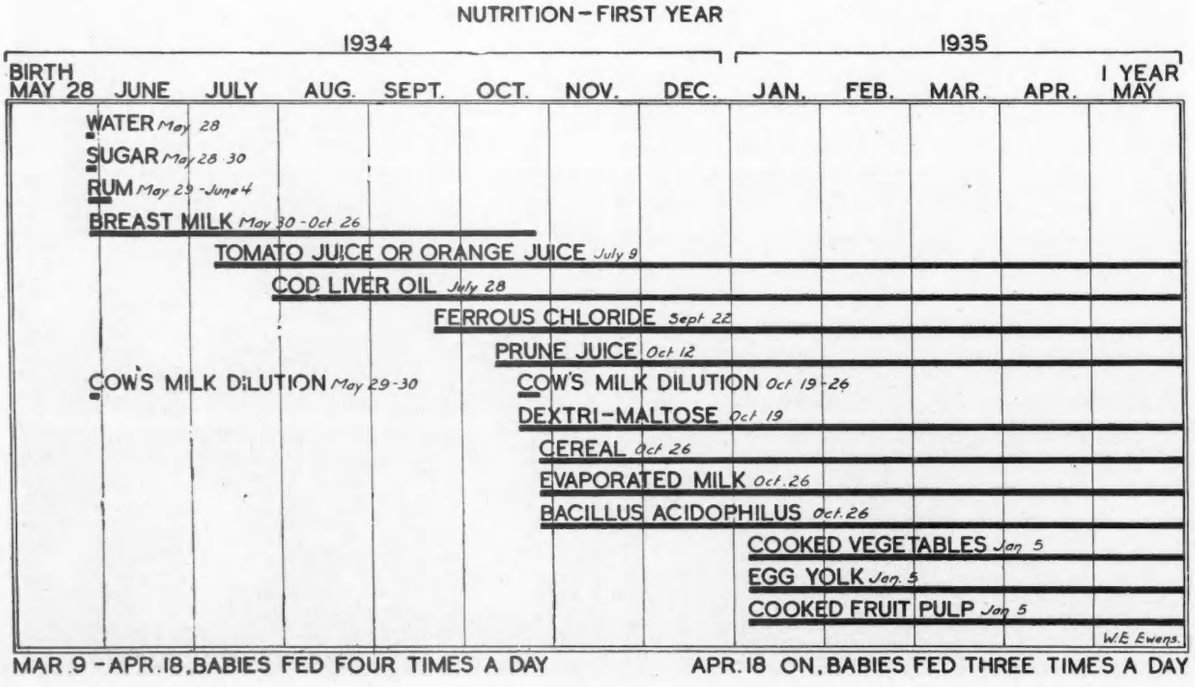


Table II.

quirements of healthy growth and easy digestion. Since the first year there has been no attempt to measure the actual caloric intake, but the normal progressive weight increase, good health, and the almost total absence of gastro-intestinal upsets, outside of infections, appear to indicate that the choice has been a satisfactory one. The menus have been varied and consisted of simple foods which have been carefully prepared. Care has always been observed to see that the foods which have been served were attractive in appearance and palatable to the taste. As a general rule the children have been hungry for their meals, but of course, they have their "off days". The

NUTRITION – SECOND YEAR

	1 YEAR JUNE	JULY	AUG.	SEPT.	OCT.	1935 NOV.	DEC.	JAN.	1936 FEB.	MAR.	APR.	2 YEARS MAY
EXTRA VITAMINES.	DAILY COD LIVER OIL ℥ ss SUMMER, ℥ i WINTER.											
	ORANGE JUICE ℥ iv DAILY.											
	FERROUS CHLORIDE. M iii T.I.D. STOPPED AT TWO YEARS – STAINING TEETH.											
CEREALS	OATMEAL, CREAM OF WHEAT, SPECIAL CEREALS.											
MILK	EVAPORATED.											
	ACIDOPHILUS B.											
						PASTEURIZED.						
MEAT	CALVES LIVER TWICE WEEKLY.											
								BACON DAILY.				
									CALVES LIVER THRICE WEEKLY.			
EGGS	CODDLED.											
							SCRAMBLED.					
SOUPS	PLAIN VEGETABLE, CREAMED VEGETABLE (PUREE), BEEF BROTH.											
VEGETABLES	PEAS, SPINACH, CARROTS, ASPARAGUS. – COOKED AND SIEVED.											
								POTATOES.				
FRUITS	APPLES, PEARS, PEACHES, IN SEASON, COOKED.											
	APPLES, PEACHES, APRICOTS, PRUNES – DRIED, COOKED.											
	BANANAS – RIPE, UNCOOKED, CUT FINE.											
DESSERTS	JUNKET, CUSTARD.											
									RICE AND TAPIOCA PUDDINGS.			
MISCELL	BREAD, BUTTER, PLAIN BISCUITS.											

Table III.

DIET SHEETS – THIRD YEAR

WEEK FEB. 1, 1937

	BREAKFAST	DINNER	SUPPER
MONDAY	CEREAL, POACHED EGGS, BACON, BISCUITS, B. BREAD TOAST, MILK.	PEA SOUP, LIVER, POTATOES, RAW CARROTS, B. BREAD, BANANAS, PINE-APPLE JUICE.	CREAM OF WHEAT, BISCUITS, MILK.
TUESDAY	CEREAL, SOFT BOILED EGG, BACON, BISCUITS, B. BREAD TOAST, MILK.	LETTUCE, CANNED VEGETABLES, CARAMEL PUDDING.	PORRIDGE, B. BREAD, MILK
WEDNESDAY	CEREAL, SCRAMBLED EGGS, BACON, BISCUITS, B. BREAD TOAST, MILK.	SOUP, POTATOES, SPINACH, BEETS, CELERY, CUSTARD.	CREAM OF WHEAT, BISCUITS, MILK
THURSDAY	CEREAL, POACHED EGGS, BACON, BISCUITS, MILK.	SOUP, RAW CARROTS, POTATOES, GREEN PEAS, GRAHAM PIE.	CEREAL, B BREAD, MILK
FRIDAY	CEREAL, SOFT BOILED EGG, BACON, B. BREAD TOAST, MILK.	LETTUCE SOUP, POTATOES, SPINACH, CARROTS, JELLO	PORRIDGE, BISCUITS, MILK
SATURDAY	CEREAL, SCRAMBLED EGGS, BACON, BISCUITS, B. BREAD TOAST, MILK.	SOUP, LIVER, POTATOES, STRING BEANS, CELERY, APPLE SAUCE.	CREAM OF WHEAT, BREAD, MILK
SUNDAY	GRUEL, POACHED EGGS, BACON, BISCUITS, B. BREAD TOAST, MILK.	LIVER, POTATOES, SPINACH, RAW CARROTS, PEAS, CARAMEL PUDDING	PORRIDGE, BISCUITS, MILK

WEEK MAY 24, 1937

	BREAKFAST	DINNER	SUPPER
MONDAY	CEREAL, SCRAMBLED EGG, BACON, B. BREAD TOAST, BISCUITS, MILK.	SOUP, LIVER, POTATOES, RICE PUDDING, BISCUITS	CREAM OF WHEAT, SUN WHEAT BISCUITS, MILK
TUESDAY	CEREAL, SOFT BOILED EGG, BACON, BISCUITS, B. BREAD TOAST, MILK.	TOMATO SOUP, POTATOES, PEAS, LETTUCE, BISCUITS, BAKED APPLE.	CEREAL, B. BREAD, BUTTER, MILK
WEDNESDAY	CEREAL, POACHED EGGS, BACON, BISCUITS, MILK	PEA SOUP, CELERY, BEETS, POTATOES, CARAMEL PUDDING, BISCUITS.	OATMEAL PORRIDGE. RUSKS MILK
THURSDAY	CEREAL, SCRAMBLED EGGS, BACON, BISCUITS, MILK.	SPINACH SOUP, LETTUCE, CANNED VEGETABLES, BISCUITS, FLOATING ISLAND DESSERT.	CEREAL, B. BREAD, BUTTER, MILK
FRIDAY	CEREAL, POACHED EGGS, BACON, BISCUITS, MILK.	VEGETABLE SOUP, CELERY, POTATOES, STRING BEANS, BISCUITS, JELLO.	CREAM OF WHEAT, ANGEL CAKE, MILK
SATURDAY	CEREAL, SOFT BOILED EGG, BACON, BISCUITS, B. BREAD TOAST, MILK.	LIVER, POTATOES, LETTUCE, ASPARAGUS TIPS, TAPIOCA PUDDING, BISCUITS.	OATMEAL PORRIDGE, BISCUITS, BUTTER, MILK
SUNDAY	CEREAL, SCRAMBLED EGG, BACON, B. BREAD TOAST, MILK.	SOUP, LIVER, POTATOES, RAW CARROTS, GRAHAM PIE, BISCUITS.	CEREAL, B BREAD, BUTTER, MILK.

FOODS USED –

1. EXTRA VITAMINES – COD LIVER OIL, ORANGE JUICE DAILY.
2. CEREALS – OATMEAL, CREAM OF WHEAT, SPECIAL CEREALS.
3. MILK – EVAPORATED – PASTEURIZED – ACIDOPHILUS B.
4. MEAT – BACON, CALVES LIVER.
5. EGGS – SCRAMBLED, SOFT BOILED, CODDLED.
6. SOUPS – PLAIN VARIED VEGETABLE, CREAMED VEGETABLE (PUREE), BEEF BROTH.
7. VEGETABLES – PEAS, SPINACH, CARROTS, ASPARAGUS, CELERY, POTATOES, BEETS, STRING BEANS
8. FRUITS – APPLES, PEARS, PEACHES, COOKED IN SEASON; BANANAS APPLES, PEACHES, APRICOTS, PRUNES, (DRIED), COOKED
9. DESSERTS – CUSTARD, JELLO; RICE, TAPIOCA, CARAMEL, GRAHAM PUDDINGS
10. BISCUITS – ARROW ROOT, SUN WHEAT, SODA, RUSKS. BREAD – WHITE, BROWN.
11. BUTTER – ON BREAD, BISCUITS, VEGETABLES.

Table IV.

nurses do not cater to their particular fancies or dislikes, and a minimum amount of coaxing is carried out. The amounts given at first are small, but they may be repeated. Fluids are given at the end of their meals. Iodized salt has been used in all cooking requiring it. The relaxation periods before and after meals appear to have been of great importance as an aid to good digestion.

INFECTIONS

The general protective measures include isolation from the public and the wearing of face masks and gowns by the attendants caring for the children. But in spite of precautions the children developed upper respiratory tract infections which are shown in the accompanying Table. They all received, as special prophylactic measures, three diphtheria toxoid injections at three-week intervals when 1½ years of age. There were no objections from the children when this very important preventive procedure was carried out. After reactions were absent, except for irritability after the first injection. Vaccinations against small-pox was performed on their thighs in January, 1937. Cecile auto-vaccinated herself on her left wrist.

The infections were practically all of the naso-pharyngeal type, and by the time that one child developed the signs and symptoms the others had already been exposed. Isolation of the first one infected did not prevent the infection from developing in the others.

PHYSICAL EXAMINATION

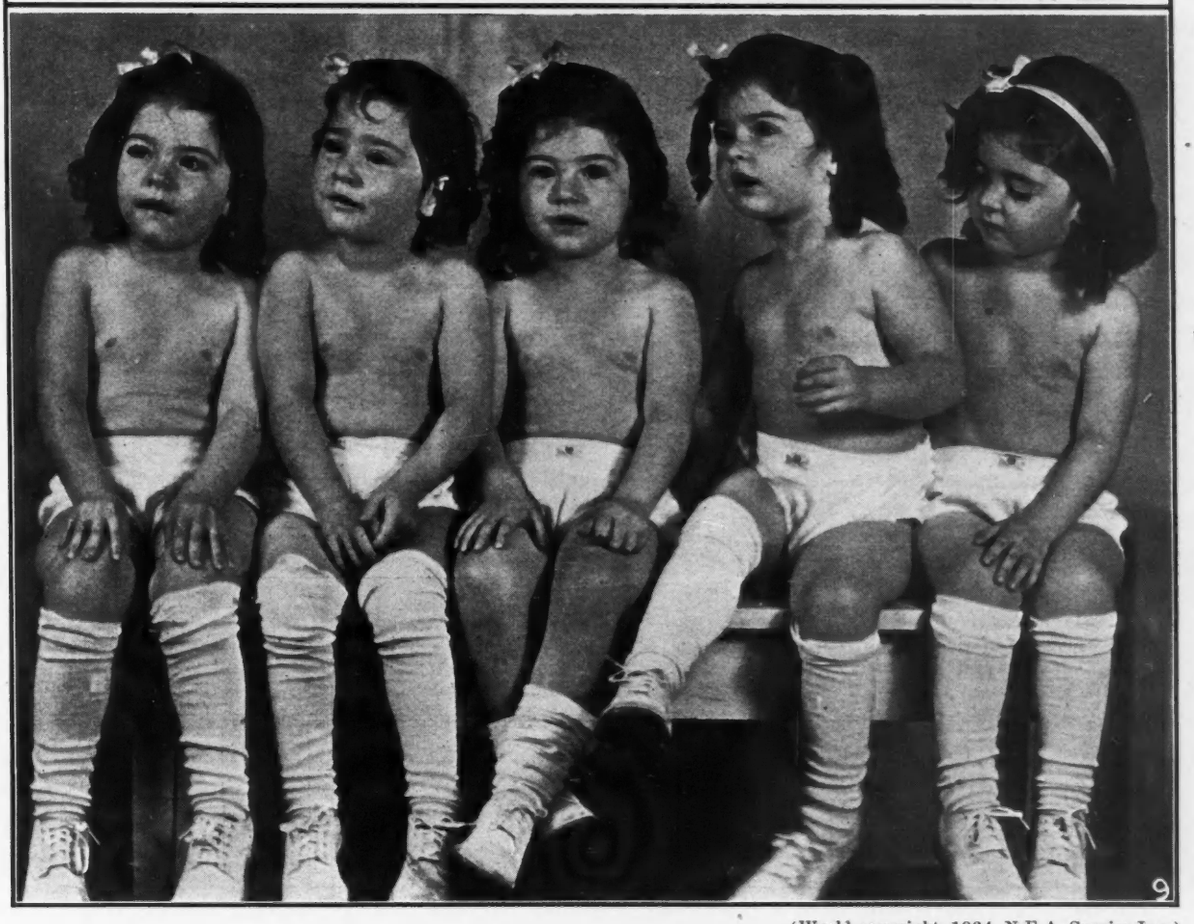
Careful physical examinations of the children have been carried out at intervals since birth. The one completed at the end of the third year showed the following general findings; good general condition and colour, firm tissues, clear lungs, normal abdomens, hearts, and nerve reflexes. Their bodies, in build, posture, muscular and bony development, appeared to be normal. All the children show the local after-results of their upper respiratory tract infections, that is, enlargement of the tonsils and other surrounding lymphoid tissue, and bilateral palpable cervical glands. The examination of their special senses found the ears and noses normal. With Yvonne, Annette and Cecile the eyes were far-sighted, but perfectly normal. Emelie has a little astigmatism in both eyes, but she may never need to wear glasses. Marie has some incoordination of the eye muscles. She does not always use both eyes equally well in looking at objects. We feel that this can be corrected.

ILLNESSES AND INFECTIONS

	1934	1935	1936	1937
YVONNE	SEPT. 15, ALL THE BABIES HAD A MODERATELY SEVERE INFECTION, WITH COUGH, NASAL DISCHARGE, TEMP. +++, MARKED DIARRHOEA, CRAMP, DISTENSION — LASTED ONE WEEK.	APR. 19-22, CORYZA, MOD. TEMP., COUGH, JULY 1-8, CORYZA, TEMP. + OCT. 7-28, CORYZA, VOMITING, TEMP. + WT. LOSS 13 OZ.	JAN. 1-6, CORYZA. JAN. 27-FEB. 6, CORYZA, VOMITING, DIARRHOEA, TEMP. 104, WT. LOSS 12 OZ. MAR. 7-15, LOOSE STOOLS, VOMITING, WT. LOSS 6 OZ. NOV. 15-19, CORYZA, LOOSE STOOLS. TEMP. + DEC. 21-27, CORYZA, LOOSE STOOLS. TEMP. +	FEB. 2-6, CORYZA, TEMP. +++ APR. 8-30, CORYZA, ACUTE TONSILITIS, CERVICAL ADENITIS, TEMP. +++ QUITE SICK. MAY 3-12, CORYZA, INJECTED THROAT, CERVICAL ADENITIS, LOOSE STOOLS, TEMP. ++
ANNETTE		APR. 19-22, CORYZA, MOD. TEMP., COUGH, MAY 9-10, TEMP. 102 (UNKNOWN ORIGIN) JULY 1-8, CORYZA, TEMP. + OCT. 3-NOV. 1, CORYZA, COUGH, VOMITING, LOOSE STOOLS, TEMP. +	FEB. 1-13, CORYZA, TEMP. + MAR. 7-12, DIARRHOEA, TEMP. +, WT. LOSS 11 OZ. NOV. 14-20, CORYZA, VOMITING, LOOSE STOOLS, TEMP. + DEC. 21-25, CORYZA, VOMITING, LOOSE STOOLS, TEMP. +	FEB. 3-6, CORYZA. MAY 15-20, CORYZA, INJECTED THROAT, CERVICAL ADENITIS, LOOSE STOOLS, TEMP. ++
EMELIE		APR. 15-20, CORYZA ++, COUGH, TEMP. ++ OCT. 6-NOV. 2, CORYZA, VOMITING, LOOSE STOOLS, TEMP. + — ++	JAN. 1-6, SLIGHT CORYZA. FEB. 2-8, CORYZA, TEMP. ++, RASH, EYES BLOODSHOT, WT. LOSS 11 OZ. MAR. 7-13, DIARRHOEA, WT. LOSS 8 OZ. DEC. 24-29, CORYZA, VOMITING, DIARRHOEA, TEMP. +	FEB. 5-7, CORYZA. MAY 15-20, CORYZA, DIARRHOEA, CERVICAL ADENITIS, INJECTED THROAT, TEMP. ++
CECILE		APR. 19-29, CORYZA, COUGH, TEMP. ++ WT. LOSS 6 OZ. MAY 12-14, CORYZA. JULY 1-8, CORYZA. OCT. 3-NOV. 2, CORYZA, VOMITING, TEMP. + WT. LOSS 1 LB.	FEB. 3-7, CORYZA, VOMITING, TEMP. + MAR. 7-15, LOOSE STOOLS. NOV. 15-19, CORYZA, VOMITING, LOOSE STOOLS. DEC. 24-30, CORYZA, VOMITING, LOOSE STOOLS, TEMP. +	FEB. 4-7, CORYZA. MAY 15-20, CORYZA, INJECTED THROAT, CERVICAL ADENITIS, LOOSE STOOLS, TEMP. +
MARIE		APR. 18-25, ACUTE CORYZA, TEMP. +++ OTITIS MEDIA, DOUBLE PARACENTESIS, INJECTED THROAT. JULY 1-4, CORYZA. OCT. 7-NOV. 1, SORE THROAT, VOMITING, TEMP. ++, WT. LOSS 11 OZ.	JAN. 4, CORYZA. FEB. 3-7, CORYZA, VOMITING, TEMP. 103, WT. LOSS 7 OZ. MAR. 7-14, LOOSE STOOLS. NOV. 15-19, CORYZA, VOMITING, LOOSE STOOLS. DEC. 21-27, CORYZA, LOOSE STOOLS, TEMP. +	FEB. 2-4, CORYZA. MAY 15, CORYZA, INJECTED THROAT, LOOSE STOOLS. TEMP. + W.E.E. Wrays.

TEMP. + — NORMAL TO 101. TEMP. ++ — 101 TO 103. TEMP. +++ — 103—

Table V.



(World copyright, 1934, N.E.A. Service Inc.)

Fig. 8.—At six months. Left to right—Emilie, Cecile, Marie, Annette, Yvonne.
Fig. 9.—At 3 years, 5 months. Left to right—Annette, Marie, Emilie, Cecile, Yvonne.

IN CONCLUSION

The general health and development of the Dionne quintuplets appear to be normal, and there is no evidence of any physical or mental abnormality resulting from their prematurity.

The Medical Guardian wishes to acknowledge the help he has received from Dr. Alan Brown. He is also appreciative of the dental survey supervised by Dr. A. D. Mason and of the examinations carried out by Dr. C. E. Hill and Dr. C. Rae.

ABSTRACTS OF STUDIES ON THE DEVELOPMENT OF THE DIONNE QUINTUPLETS

PREPARED BY W. E. BLATZ

Professor of Psychology, University of Toronto

THE following are abstracts of six of the papers presented at the Conference on the Research Studies on the Dionne Quintuplets, held at Toronto on October 30, 1937.

I. A BIOLOGICAL STUDY OF THE DIONNE QUINTUPLETS—AN IDENTICAL SET*

The scientific interest centres about the question of the embryological origin of these five children. The authors present the thesis that they are monozygotic quintuplets and give the following three points to substantiate their claim. (*a*) From all the evidence available there was only one chorion. (*b*) An examination of the five with reference to their hereditary characteristics shows a remarkable degree of similarity (see below). (*c*) The age of the mother at the birth of the children, and the absence of evidence of twinning in the family history for three previous generations suggests a monozygotic origin.

The evidence presented to substantiate point (*b*) is as follows. Palm prints, finger prints were meticulously analyzed and the results were recorded. Table I is an excerpt from a larger table which shows how closely the quintuplets approximate each other in ridge-count, and how they differ from their three siblings. The five have a count of approximately 100 with a total variation of ± .3 and the siblings vary from 69 to 139.

TABLE I.

FINGER PATTERN TYPES

	Quantitative value		
Emilie	44		55
		99	
Yvonne	58		44
		102	
Cecile	47		53
		100	
Marie	52		49
		101	
Annette	51		50
		101	
Ernest	31		47
		78	
Rose	28		41
		69	
Therese	60		79
		139	

* MacArthur, J. W. and Ford, N.: University of Toronto, Child Study Series, No. 11.

TABLE II.

Characteristics of the blood groups, eye, skin, and hair of the quintuplets. Iris colour was matched with Saller's chart; iris pattern with Hesch's series; and skin and hair colours with Schultz' table

	Blood group	*Iris colour*	*Iris pattern*	*Eye refractive error*	*Eye lashes*	*Eye brow*	*Hair colour*	*Hair form*	*Hair whorl*	*Skin colour*
Emilie	O	M_4	9	+1.25	long curled dark brown	light brown	8	wavy	counter clock-wise	3
Yvonne	O	M_4	9	+0.75	long curled dark brown	light brown	8	wavy	counter clock-wise	3
Cecile	O	M_4	9	+0.75	long curled dark brown	light brown	8	wavy	counter clock-wise	3
Marie	O	M_4	9	+1.25	long curled dark brown	light brown	8	wavy	clock-wise	3
Annette	O	M_4	9	+0.75	long curled dark brown	light brown	8	wavy	counter clock-wise	3

In Table II various characteristics are enumerated, and a description for each quintuplet is included. Except for the difference in refractive error for Emilie and Marie and the clockwise direction of the hair-whorl in Marie the five are identical.

Interrelations of the members of the identical set.—It is an intriguing problem that by locating the especially close resemblances within the set, and perhaps employing the concept of asymmetry reversal as in the armadillo and in twin materials (Newman, 1931) one might reconstruct the details of the formation of the five embryos from one ovum, discover the times and the precise order of their separation, and trace their former positional relations to each other at successive stages of their development. There is doubt whether this can be successfully done at present.

Though all are much alike in dermatoglyphic characters, the pairs most similar in their left palms are C and M, Y and A; in the right palm, C and Y. Such relations might suggest a certain sequence of separation.

Although resemblances may be cited which appear at random rather than correlated, yet in an unusual number of respects E and M are in some way paired off, being smallest at birth, somewhat lagging in growth, having slenderer faces and more sloping palates, in their strabismus and in left sole prints; and, as if they might be products of a late division, they show some cross resemblance in their palms, and are the only pair which show the combination of reversal in both hair and handedness. Two others, Y and A, are much alike in facial form, ear shape and in the left palms. C and M show likenesses in shape of ears and in the left palms; C and Y, in their right palms. These relations may be described in a diagram:

$$\begin{matrix} E-M \\ \quad\quad > C \\ A-Y \end{matrix}$$

This suggests the linking of the whole set in a continuous chain of marked similarities, the circle to be completed by connecting E and A directly or through the hypothetical sixth embryo. Possibly there is some relation between resemblances and corresponding degrees of retardation in development.

As would be expected, most of the characters are inexactly inherited and the variations are largely random and unpredictable.

That the Dionne quintuplets are a set composed entirely of identicals and derived from a single ovum is the main conclusion reached from the consideration of those biological characters which it has been possible to study. The evidence leading to this conclusion has been drawn from several sources:

1. *The nature of the fetal membranes.*—Though the afterbirth was destroyed, the published descriptions of it report only one placenta and one common chorion; observers differ as to whether there were five amnia and five cords attached close together, or one amnion and one cord with five branches. According to either description, the placenta is that characteristic of a monozygotic set.

2. *The close resemblance of the quintuplets* in a great number of hereditary characters, some of them rare or extremely developed. This evidence is considered to be partly direct and positive (when the sibs are available as controls), and partly supporting or not contradicting the diagnosis (when the corresponding sib characters could not be studied).

Besides being of the same sex, the quintuplets all have the same blood group (O), and are nearly indistinguishable in eye colour and pattern, hair colour, texture and form, and in degree of skin pigmentation. The sibs vary over a wide range in eye colour, hair colour and form, and complexion; their blood groups are not known. The quintuplets are so confusingly alike in facial features that few can consistently identify them correctly, except after becoming acquainted with small individual variations in the form of the face, ears or teeth. Particular emphasis was laid on the likeness of the finger, palm and sole prints, since these characters are fixed and constant throughout life.

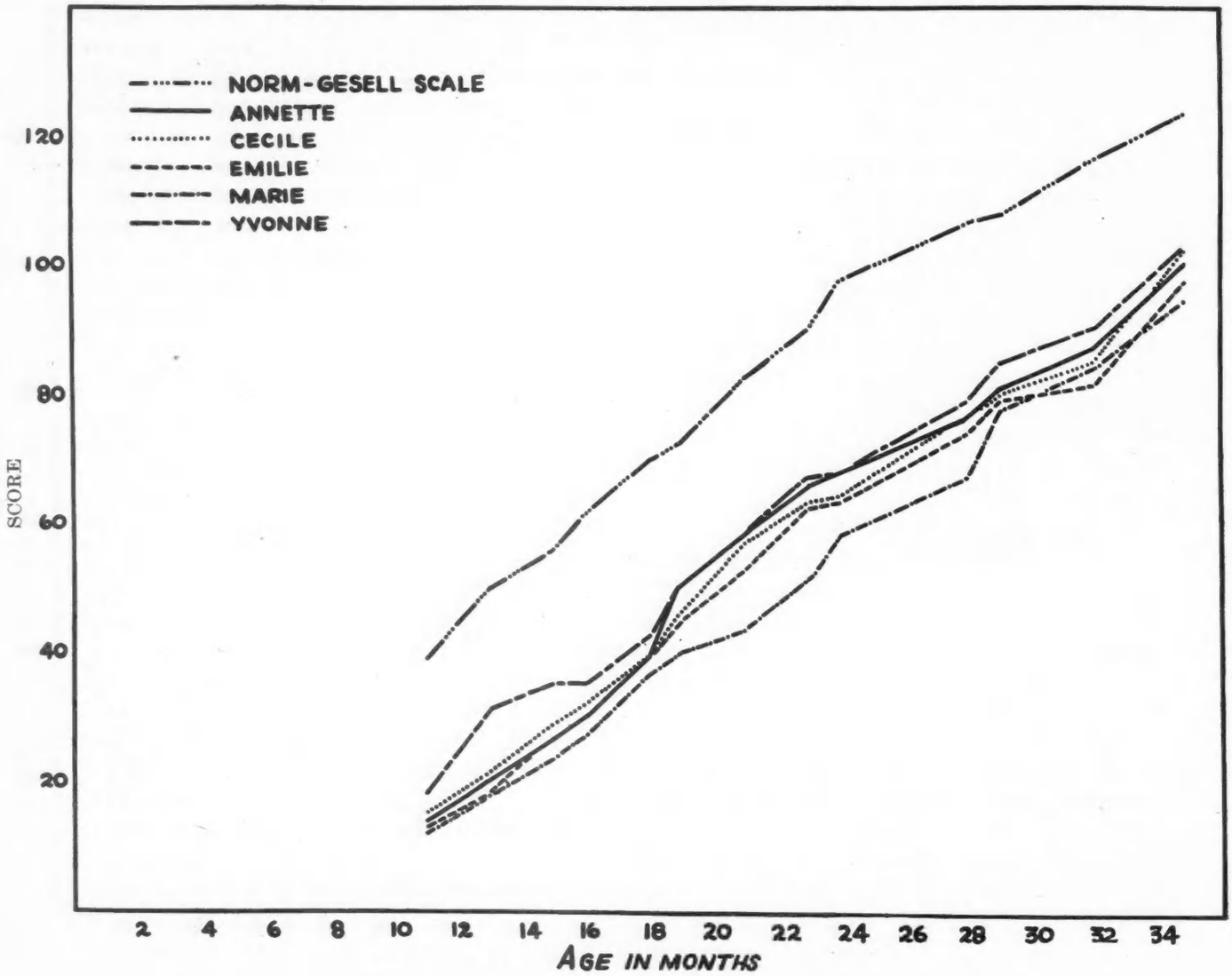
In addition to a general resemblance (as close as that found in identical twins) in their ridge-counts, lines and patterns, the quintuplets also share rare features, such as a mild form of syndactyly of the second and third toes, thenar patterns on the soles, and whorls among the palmar interdigital patterns.

Throughout the set the two hands of any member are less alike than is one of her hands like a hand of a sister. In sib comparisons the opposite is the case.

It was shown by an objective quantitative method that the quintuplets or any pair among

CHART 1.

MENTAL DEVELOPMENT OF QUINTUPLETS.



them are as alike as identical twins; the sib comparisons show twice as much difference.

Such close resemblance as the quintuplets show in many characters would not be expected, unless the five all carry the same inheritance.

Interrelations among the group indicate a bond between E and M (the only pair showing both hand and hair reversal), and a relation between M and C, C and Y, Y and A. It is possible that the gap between A and E might have been bridged had the possible sixth embryo survived.

3. Additional evidence, which some will accept as supporting the diagnosis of monozygosity, is found *in the youth of the mother* and the absence of any inherited proclivity to production of twins or other multiple births in the immediate family.

Some 60 other cases of quintuplet births have been traced in the medical literature. Those which are completely described show an irregular sex-distribution, a high proportion of males (110 ♂♂: 90 ♀♀), and a high percentage (40) of same sexed sets. At least three sets appear to have been identical; these are characterized also by lack of history of twinning and by the low age and parity of the mother. The mothers of fraternal sets were older and had borne an unusual number of twins or triplets at other births.

The Dionne quintuplets are unique in having survived as an unbroken set, the achievement being made possible by the practice of modern

pædiatrics and the untiring efforts of their attending physician and his aides.

II. The Mental Growth of the Dionne Quintuplets*

Intelligence tests were administered to the quintuplets regularly at two month intervals from the 11th to the 36th month. The Gesell tests were used throughout. The results are shown in Chart 1. As may be seen, the five children fall short of the norm for their chronological age. There are two factors which would influence their score and give the appearance of retardation. (*a*) These children were at least two months premature. In such cases they usually do not recover the normal score until the fifth year. (*b*) Since language becomes an increasingly important skill with increasing age, the marked retardation in this capacity accounts for the low score in the intelligence tests.

The order of mental development remains fairly constant after the first few months, with Yvonne at the top, then Annette, then Emilie, then Cecile, and finally Marie. Marie was the smallest at birth and appeared to suffer most from the handicap of prematurity (Chart 2).

The Gesell Test is divided into four divisions, Motor, Adaptive, Personal-Social and Language tests.

In the motor tests the five children most closely approximated the norm. In the adaptive and personal-social they were retarded from 2 to 4 months. In the language tests the retardation was nearly 12 months (see below).

An analysis was made of the rate at which the five children were accelerating in their mental development. Chart 2 shows that, compared with the speed of development of average children, these five are accelerating at a greater rate. Thus they are passing relatively more tests at increasing age-intervals. This shows that they are catching up. One cannot predict when this acceleration will slow down, but with the acquisition of language it may be foreseen that soon they will arrive at the normal rate of development and establish their position on the scale.

* Blatz, W. E. and Millichamp, D. A.: University of Toronto, Child Development Series, No. 12.

III. The Early Social Development of the Dionne Quintuplets*

Nothing has more stirred the imagination than the speculation on what the experience would be, of living together with four other sisters of exactly the same age. Quite aside from this human interest is the scientific curiosity concerning the individual social development of these five sisters. Taking for granted their common heredity and their apparent identity, one might ask whether they would manifest the same social traits and similar social behaviour, or differ widely in these characteristics.

It might be argued that these sisters are living in the same social environment, and hence should manifest the same traits. However, one must consider that the environment, in a social sense, is determined not only by the physical surroundings and the contiguous human beings but also is a function of the individual's own response to the environment. This behaviour colours every subsequent reaction and thus grows on itself. Then, one is not surprised to learn that these five children are already showing marked differences in social behaviour.

Observations were begun at twelve months of age. The children were placed in a play pen in pairs and the number of social contacts were recorded and later analyzed. The categories into which each contact was placed depended upon whether it was initiated by a child, responded to, or ignored. Later the children were observed when they were all together in a group of five. By this means the total number of social contacts could be determined. Chart 3 shows in profile the total number of contacts which each child directed towards each of the other four children, and also the number which were received by each child.

Certain definite conclusions may be drawn from these data.—

(*a*) The total frequency of social contacts increases with age.

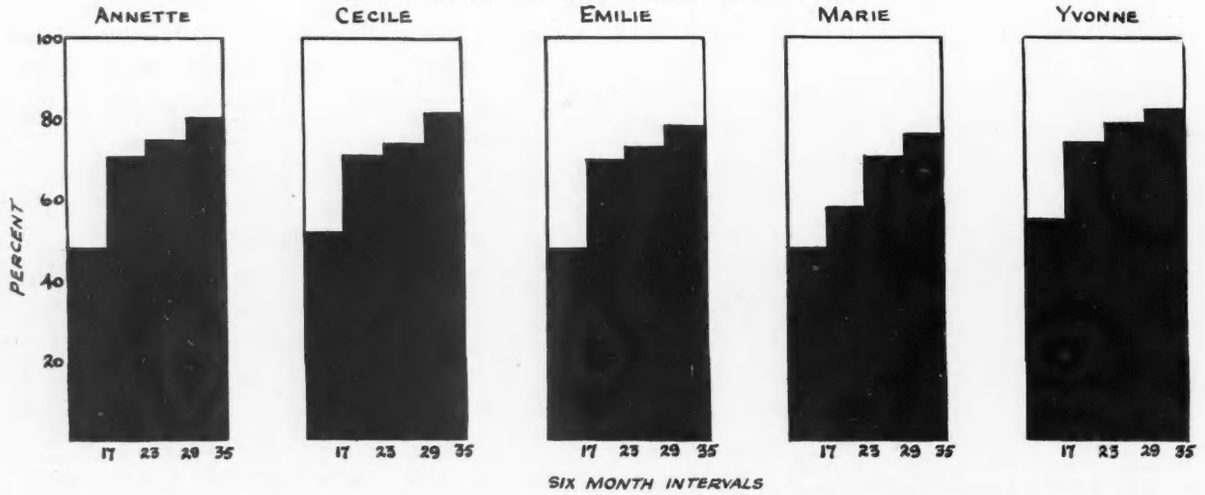
(*b*) There are definite individual differences which are becoming more marked with reference to each child:— (1) Annette and Cecile show the most contacts both "to" and

* Blatz, W. E., Millichamp, D. A. and Charles, M. W.: University of Toronto, Child Development Series, No. 13.

"from"; (2) Emilie shows the least; (3) Annette and Cecile have most to do with each other socially; (4) Emilie and Yvonne have least to do with each other. If one were to check the number of times each child *initiated* a contact towards another child, the following would be shown:— (1) Annette initiates most contacts, in other words, makes most overtures to the other children; (2) Yvonne initiates fewest. But if we were to count the number of "responses" which these initiated contacts elicited one would find that Annette would receive relatively fewer than Yvonne. In other words, although Annette tries harder, her return in social contacts is less than that of Yvonne, who tries least of all. Emilie is mid-

CHART 2.

SHOWING THE PERCENTAGE OF THE TOTAL POSSIBLE MENTAL TEST SCORE PASSED BY EACH CHILD AT SIX MONTH INTERVAL.



way on the scale. Her score is about fifty-fifty. Marie has the least absolute number of responses.

The second trend which is apparent from this chart is the stability of the social behaviour of these five children as compared to a control group of the same age. The profile slope remains fairly constant. This may be due to the circumscribed social grouping in which these children live.

From the point of view of the psychologist, the most interesting aspect of this paper is that to date the children have shown, according to this method of recording, decided and individual traits of social behaviour. It will be interesting to watch how they respond to the new social contacts which they will inevitably make as their social behaviour expands to include other children.

IV. THE DEVELOPMENT OF SELF-DISCIPLINE IN THE DIONNE QUINTUPLETS*

The most important aspect of personality is the attitude one develops toward authority and the control one establishes over the emotions of fear and anger.

As soon as the children were no longer under the meticulous scrutiny of the doctor and the nurse and their survival within normal risks was assured, the disciplinary procedure as employed at St. George's School for Child Study was inaugurated by Dr. Dafoe. In brief this plan may be described as follows.† A concept of discipline which is educational rather than punitive; the development of responsibility in children by expecting them, after an adequate period of instruction, to assume responsibility for looking after their own needs; an arrangement of the physical surroundings such as to stimulate initiative and adventure, without being too exacting with reference to the necessary skill for manipulation, and eliminating danger situations beyond the capacity of the child to deal with them; a type of supervision which permits emotional development and maturity rather than suppression on the one hand or lack of control on the other; an attitude of serenity on the part of adults, accompanied by the example of pleasurable industry.

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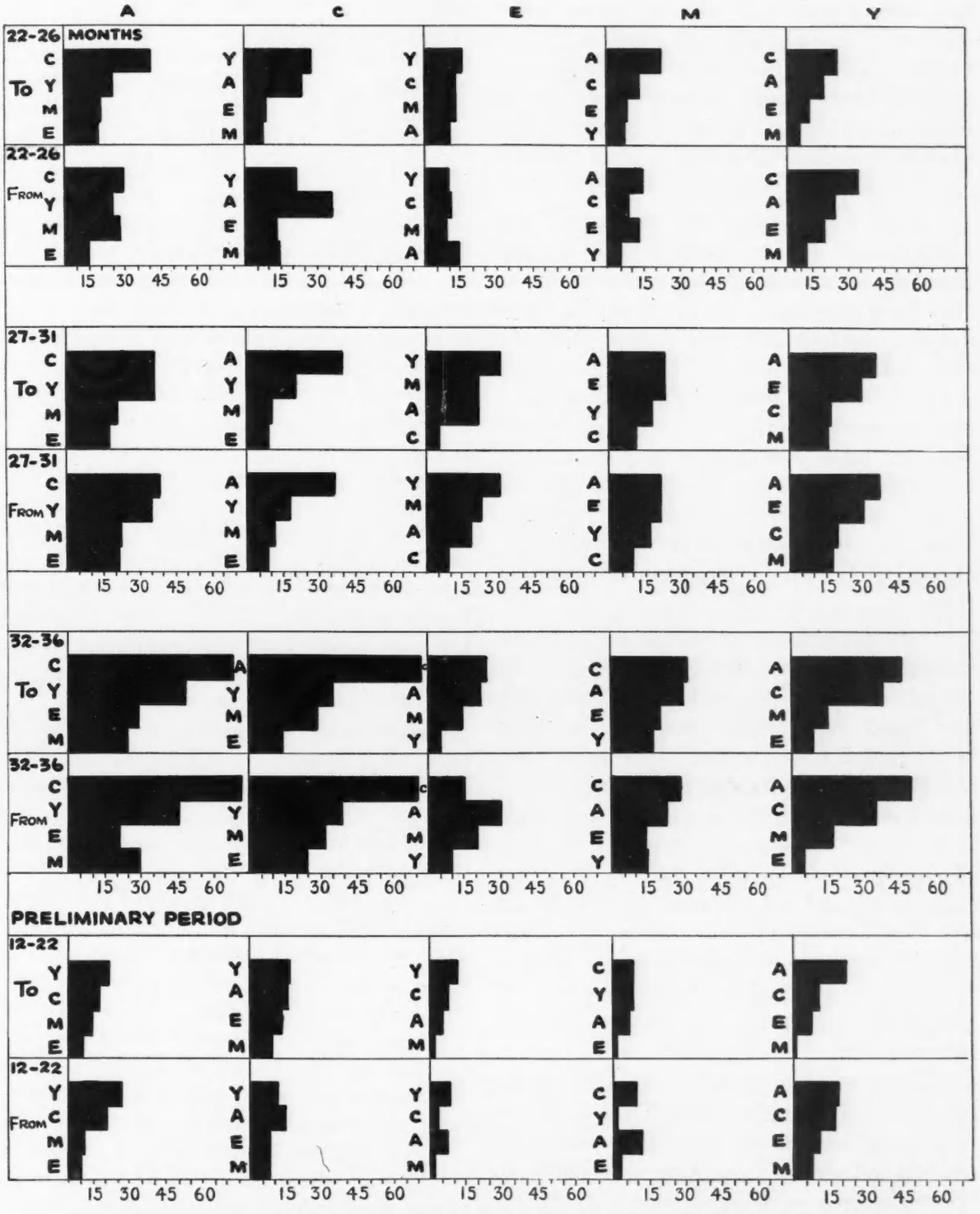
* Blatz, W. E., Millichamp, D. A. and Chant, N.: University of Toronto, Child Development Series, No. 14.

† *cf.* Nursery Education: Blatz, W. E., Millichamp, D. A. and Fletcher, M. I.: Wm. Morrow Co., 1935.

CHART 3.



SHOWING IN PROFILE THE NUMBER OF CONTACTS DIRECTED BY EACH CHILD TO EVERY OTHER CHILD AND THE NUMBER RECEIVED BY EACH CHILD FROM EVERY OTHER CHILD

Under this scheme of training some very interesting facts were brought to light.

1. Since "obedience" as an end in itself was not a desired goal, these children on many occasions were non-compliant in their attitudes. This is a desirable trait, since compliance, complete and unquestioned, makes for a conformist, a reactionary and a dullard. But there were marked individual differences. Thus, Annette was the most non-compliant and Emilie the least.

2. Since at times some form of arbitrary consequences had to be arranged, especially in social situations, the number of times such disciplinary procedures were employed was recorded. Thus Annette required such interference relatively least and Emilie most. One may infer from this that Annette was using a non-compliant form of behaviour as a form of social aggressiveness, but made sure not to go too far. In Emilie's case, when she was non-compliant she usually *meant* to be and would go the limit. These data correspond with the conclusions drawn in the study on social contacts reported above.

In the training in emotional control these children showed the same tendencies as do average children. The frequency with which they "lost their temper" decreased markedly in the period from the first to the third year. Since this form of behaviour is largely due to frustration of desires of some sort, a decrease in frequency indicates two influences at work, (1) non-interference on the part of the supervising adult, and (2) increased skill in dealing with the physical and social environment. The remarkable fact was evidenced in the records that these children show a low frequency of quarrelling as compared with single children of their own age.

The five children manifested very few instances of fear in their second and third years. Since their environment has been arranged to eliminate all serious physical dangers, and since they have been accustomed from birth to see strangers about them, this tendency is not to be wondered at. However it may be suggested that in the near future arrangements will have to be made for a wider social and physical experimentation.

V. Routine Training of the Dionne Quintuplets*

After all, the fact that there are five rather than one or two does not alter the technique by which the children are to be brought up. These children had to learn how to feed themselves, how to go to sleep, how to control their eliminative functions, etc., exactly as do other children. For the first year the infants were under special care for reasons of health and because premature children need more attention than full term children. After it became apparent that they were to develop into robust, healthy children the *pro tem* of their routine training was attacked. The rules and regulations as laid down by modern pædiatric and child-care practice were rigorously adhered to. The results were very encouraging, especially with reference to sleeping and washing and dressing.

There was considerable difficulty in connection with the training of bowel control. Undoubtedly because of a physical condition these children had frequent and unformed stools until well on to the end of the second year. Any attempt to train control under these circumstances was unwise, so that a plan of education was postponed until this condition seemed alleviated. By the use of suppositories at regular intervals, anticipating the time for evacuation as learned from the charts, a beginning was made at regulation. An exacerbation of the difficulty intervened and training was postponed until the third year, which resulted in success. By the end of the third year the children were trained comparably to their age.

As was to be expected, with the delay in bowel control the control of bladder elimination was also delayed. But after the former routine began to show signs of self-regulation the training in day-time bladder control was instituted. This plan resulted in a rapid learning. At three years of age the children were dry during the daytime and only occasionally wet at night after being picked up at ten o'clock.

The eating routine was difficult at first because the children, having to be fed, gave the nurses considerable trouble because one resented being left aside while another was being fed. However, as they grew older and learned to

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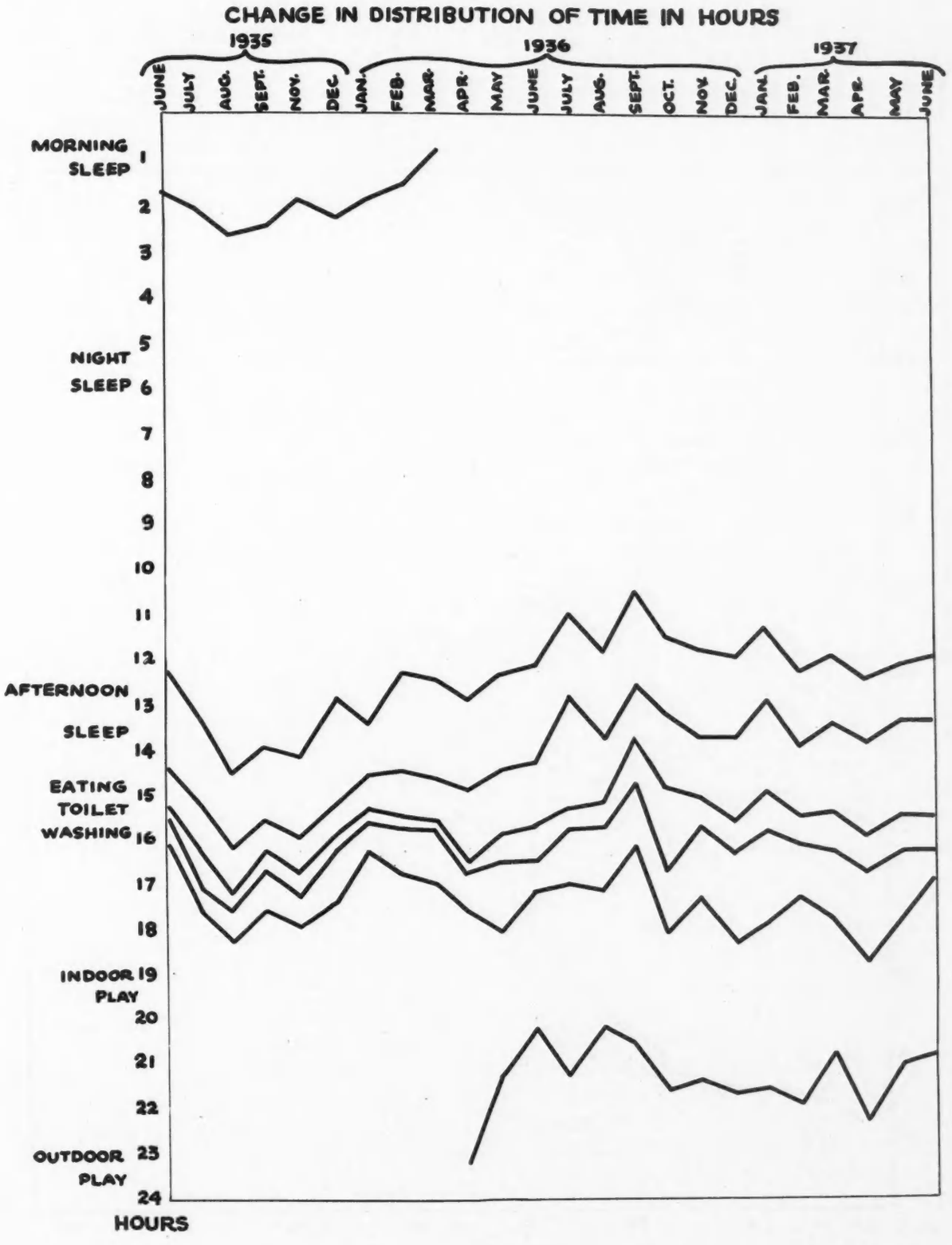
* Blatz, W. E., Millichamp, D. A. and Harris, A. L.: University of Toronto, Child Development Series, No. 15.

CHART 4.

DAILY ROUTINE ACTIVITIES.

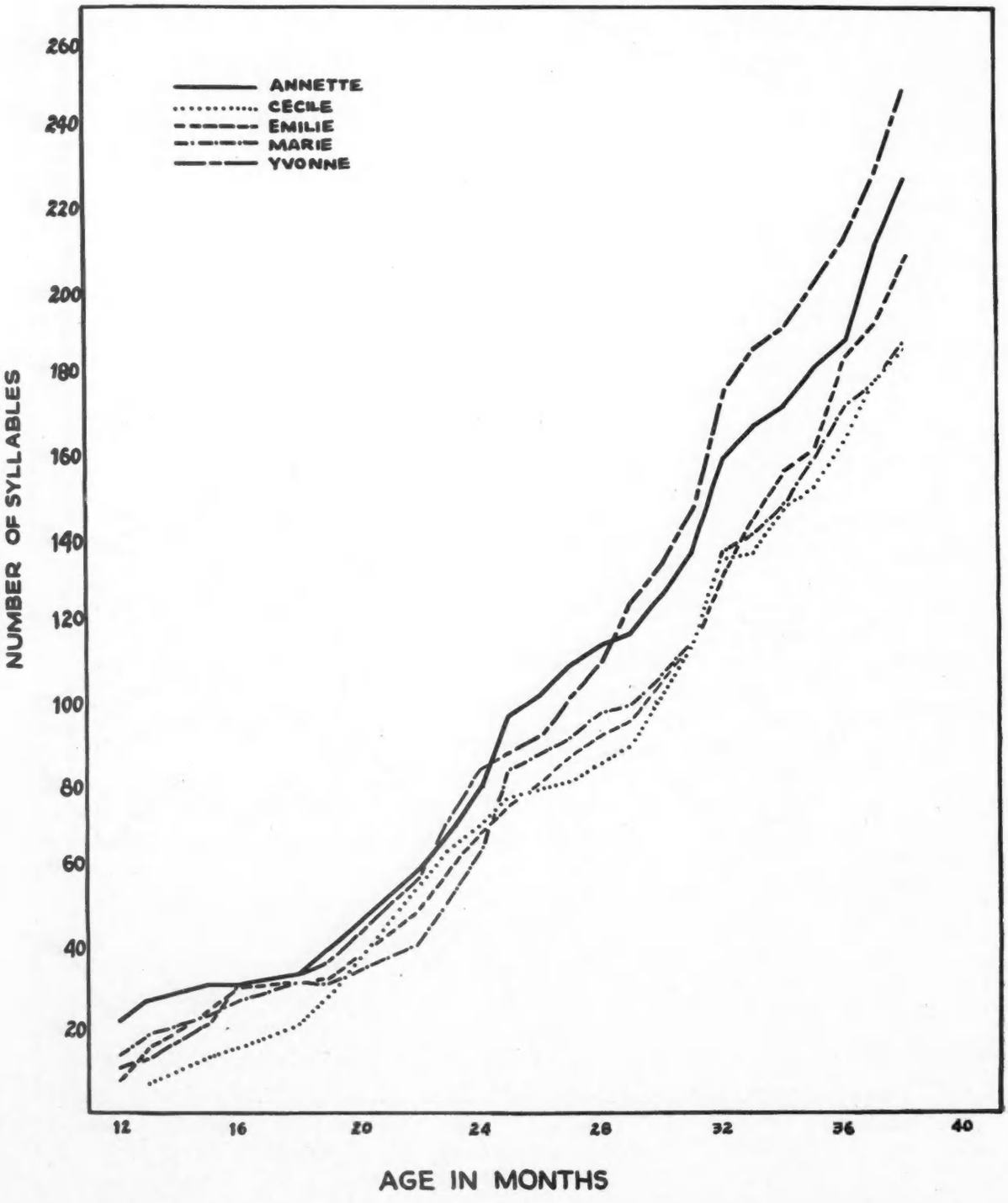


drink from a cup and to feed themselves with a spoon the difficulties diminished. The plan now employed is for the five to sit at small tables in a room set aside as a dining room. They serve themselves from a separate table, clear up their dishes, and of course feed themselves without any assistance from adults.

Considerable anxiety was felt as to the effect of the observation period, when thousands of spectators view them, upon the five children. After the age of two years, the observation building now in use was built. This is a U-shaped structure built around a nursery-school playground. The inner wall of the building is

CHART 5.

PROGRESS IN SYLLABLIZATION.



screened so that the spectators may see the children but remain invisible. Although it is obvious that the children from time to time are aware of being under scrutiny, it is surprising how little this seems to affect their behaviour. Their activity and independence is well up to the standard of children of their own age.

In September, 1936, their indoor play was arranged as in a nursery school, half free play with dolls, blocks, dolls' furniture, dishes, etc., and half controlled play in a separate room, where they learned to use constructive materials, such as plasticine, crayons, paint, coloured blocks, chalk, etc.; also a story hour with picture books, and the music hour with songs and dances to the piano, and selected music played on the gramophone.

In general one may say that to the observer these children throughout the day follow a routine ideally suited for their age. Regularly this routine is altered to suit their growing needs (see Chart 4). The amount of time spent in the various routines varies with age and weather, etc. Thus the children are sleeping less now than two years ago. Outdoor play is increasing in amount. More time is spent at washing and eating and dressing because they are helping themselves. Although this all appears as if these children were being hemmed in by restrictions and regulations, anyone who has visited knows them to be happy, contented, and spirited youngsters, aptly using the materials at their disposal for their enjoyment and advancement.

VI. The Early Development of Spoken Language in the Dionne Quintuplets*

As indicated in the study on the mental development of the quintuplets they were quite retarded in the use of spoken language.

There are several studies in the field of language development, notably that of Day,† which point out that twins are backward as compared with single children. This was also discovered by a control group studied at the same time as the "quints" were being observed. Hence one would expect to find this phenomenon exaggerated in the quintuplets. It was quite obvious to the authors that the quintuplets, at 12 months of age, were using sounds and grunts and particularly gestures to communicate their wants among themselves as well as to the adults in charge. This use of gestures and pantomime still continues and accompanies their speech.

A compilation of the syllables used was made every month. The Chart illustrates that at twelve months they were using from 8 (Marie) to 23 (Annette) syllables. This corresponds to the six-month level of an average child. Words were not used as intelligible sounds until the 19th month (Annette) and the 22nd month (Cecile). By the end of the third year the children had used from 170 to 260 syllables and 185 words in all. The rate of growth in word use is much slower than the rate of syllable use. From the rapidity with which these five children are progressing one may predict that they will approximate the norm by their fifth year as is usual in such cases. In order that the children should be bilingual, in September, 1937, specific training in English was begun by speaking the language at midday meal daily. Observation of the learning progress in this skill will be recorded.

This study is a preliminary report and will be supplemented by the data in sentence construction, and use of word-order, etc., in the near future.

The probable cause of delay in the use of spoken language may be conjectured as follows.

Since language develops where the need is felt, it was apparent that these children in infancy received such excellent care that every need was *anticipated*. Language was not necessary.

Since their multiple births provided a social "group" from birth, the communication necessary for social intercourse remained at an infantile level, as is true of twins.

The slower rate of development of words than syllables indicates that skill in vocalization precedes the actual application of this skill to *use*. This fact bears out the first contention. Further, since there were no other children about to provide a stimulus for further experimentation, the syllables themselves remained relatively unvaried in form. Adult speech is not so efficacious in stimulating language as are other children at this age level.

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* Blatz, W. E., Fletcher, M. I. and Mason, M.: University of Toronto, Child Development Series, No. 16.

† Day, Ella J.: The development of language in twins, Child Development, Vol. III, 1932.

AN ATTEMPT TO INHIBIT THE DEVELOPMENT OF TAR-CARCINOMA IN MICE

(THIRD REPORT)

THE EFFECTS OF VITAMINS ON THE TUMOUR THRESHOLD

BY J. R. DAVIDSON

Winnipeg

IN two preliminary reports[1, 2] the following observations were made (Table I): (1) tumour growths can be produced by tar-irritation; (2) mice with tumour growths show impairment of normal reproduction; (3) when mice were fed on a diet higher in vitamins than the ordinary diet the growth of tumours seemed to be retarded and the average length of life somewhat increased.

In the present study an attempt was made to follow up the observations on vitamins by using a synthetic diet. It seemed advisable also to use a control synthetic diet which would produce an animal the facsimile, as nearly as possible, of the original parents. After I tested out on a series of animals synthetic diets with vitamins arranged in different ways, both singly and in combination, and with varying dosage, the following two diets were selected for this study.

CONTROL DIET

Similar to Evans "E" free diet, with ½ ounce of wheat germ oil added. The following makes about 25 oz. of ration.

Casein	7	oz.
McCallum salts	1	"
Brewer's yeast	2½	"
Cod liver oil	½	"
Wheat germ oil	½	"
Lard (fresh)	4½	"
Cooked corn starch	14	"

HIGH VITAMIN CONTENT DIET

This diet has a higher vitamin content (HVC).

Casein	7	oz.
McCallum salts	1	"
Brewer's yeast	5	"
Cod liver oil	½	"
Wheat germ oil	1	"
Lard (fresh)	3½	"
Cooked corn starch	14	"

Three drams of a highly concentrated vitamin "A" (30,000 international units per g.) were added.

It will be observed that the higher vitamin content diet is similar to the control diet, except that the vitamins A, B and E are increased, and the lard slightly reduced.

The animals selected for this study were bred from two mice which, on biopsy, had shown the presence of tar-carcinoma. The offspring were divided into seven divisions and bred and raised in different ways (Table II).

Divisions 1 and 7 were treated with tar to produce tumours and then bred. This was done to retain control mice whose standard of anatomical structure and physiological function would represent, as nearly as possible, the two original mice of the series. It was observed in the early part of this experiment that if the offspring experienced the same internal and external environmental conditions as the parent mouse the same standard of resistance to tumour growth was maintained.

There was no mating in division 2. Later the male mouse was replaced by the tarred male in division 1, as there was no corresponding male available. It was deemed advisable, if possible, not to raise the standard of physiological function of the animal so that the second generation of division 2 was dropped from a treated (*i.e.*, tarred) male and untreated mothers. There were sufficient females in the offspring dropped to divide, and these were used in this series.

The other divisions, 3, 4, 5 and 6, untreated mice, were allowed to breed naturally, so that by the time the offspring of divisions 1 and 7 (control mice) was ready for the series, there were from 2 to 4 generations dropped from divisions 2, 3, 4, 5 and 6, as shown in Table II. The last generation of the divisions was divided into two groups, group (*a*) and group (*b*). Group (*a*) was placed on control diet and group (*b*) on the diet higher in vitamin content. All mice were tarred every third day for 27 tarrings, as this was judged from experience to be about the necessary amount of tar-irritation required to produce growths in this particular strain of control mice.

On May 28, 1937, thirteen days after the last tarring, growths were sufficiently developed in the control mice, group (*a*), division 1, and group (*a*), division 7, to be removed for biopsy.

TABLE I.

Pen	*Mice*	*Diet*	*Tarring (months)*		*Carcinoma present at death*	*Average life of mouse (days) after discontinuing tarring (DT)*
1932					Percentage	
1.	16 M (male)	.....	5	Showing the effect of a mixed household diet on mice of unknown susceptibility to tar-carcinoma.	35.0	.....
2.	16 F (female)	.....	5		6.4	.....
3.	20 M	.....	4½		55.0	128.14
4.	20 F	.....	4½		45.0	158.6
5.	10 F	.....	4½		20.0	173.8
6.	9 M	.....	4		66.2	177.1
7.	21 F	.....	4		38.2	94.20
8.	24 M	.....	4		30.10	60.6
9.	12 F	Vitamin E administered for breeding.	4		75.0	104.5
10.	11 F		4		54.0	102.8
	——>			Impaired reproduction.		
11.	9 M		4		25.0	79.2
12.	9 M	.....	4		20.0	100.4
13.	8 F	NHVC	4	Two natural diets were arranged, one high and the other low in vitamin content: (1) High vitamin content (NHVC): milk, lettuce, wheat germ cereal, whole wheat bread, lard, and wheat germ oil. (2) Low vitamin content (NLVC): milk, carrots, oat-chop, white bread and lard.	100.0	180.3
14.	12 M	NHVC	4		75.0	162.11
15.	11 M	NHVC	4		60.0	153.5
16.	11 F	NHVC	4		81.8	269.1
17.	10 M	NLVC	4		100.0	100.7
18.	10 F	NHVC	4		100.0	331.7
19.	10 M	NHVC	4		80.0	326.5
20.	12 F	NLVC	4	Biopsy at 4½ months 100 per cent.	100.0	125.2
21.	10 M	NLVC	4	" " " " " " "	90.0	123.0
22.	10 M			(Reserved for breeding purposes.)		
23.	10 F	NLVC	4	Biopsy at 4½ months 100 per cent. Then changed to NHVC diet.	100.0	153.9
24.	10 F			(Reserved for breeding purposes.)		
25.	14 M	NLVC	3-10	Biopsy at 3½ months 100 per cent.	100.0	110.2
26.	14 F	NLVC	3-10	" " " " " " "	100.0	137.6
27.	12 M	NLVC	3-10	" "3-18 " " " "	100.0	161.2
28.	12 M	NHVC	3-10	" " " " 30 " "	100.0	183.3
29.	8 F	NHVC	3-10	" " " " 50 " "	100.0	173.3
30.	7 M	NLVC	3-10	" " " " 100 " "	100.0	102.0

Unfortunately, there remained only four mice in group (*a*), division 1, as all the others except one were destroyed by vicious mice in the group. Another mouse was killed by the others the day after biopsy, so the remaining three were placed in separate pens. Biopsy of all four showed grade 1 epidermoid carcinoma. Growths in group (*a*), division 7, with the exception of one, showed marked differential changes towards epidermoid carcinoma. The few growths that appeared in the other groups were quite small and were left to develop and to be taken at a later date. June 28, 1937, one month later, all growths present on the mice in the other groups were removed.

Table III records the number of growths found in each group, the histological findings, and the number of remaining mice. A few mice died in the different groups as follows.

Group (*a*), division 1.
Original No. 8 (M). One died after tarring. Four others were destroyed by mice in the group, leaving only three male mice in this group.

Group (*b*), division 1.
Original No. 7 (M and F). One male was found dead June 23, 1937, cause unknown. No growth.

Group (*b*), division 3.
Original No. 6 (M). One was found dead May 9, 1937; another May 17, 1937, cause unknown. No growth on either mouse.

Group (*b*), division 4.
Original No. 8 (F). One mouse died June 14, 1937, cause unknown. No growth.

Group (*b*), division 5.
Original No. 6 (M). One died after sodium sulphide treatment; another May 28, 1937, cause unknown. No growth.

Group (*b*), division 6.
Original No. 7 (M). Two mice died June 18 and 20, 1937, cause unknown. No growth on either mouse.

Most deaths occurred during hot days. It is difficult to prevent male mice in groups from fighting.

It was noted early in this experiment that impairment of reproduction occurred among mice under treatment which developed tumour growths. When the mice with tumour growths were placed on synthetic diets and tested out, it was found that *not one vitamin but a com-*

TABLE II.

TWO MICE WERE SELECTED FROM A GROUP SHOWING 100 PER CENT CANCER FOR SEVERAL GENERATIONS

M. mouse. Biopsy Epidermoid carcinoma. — These mice were bred twice. The offspring were divided into seven divisions and each division fed on the diet as below indicated. — F. mouse. Biopsy Epidermoid carcinoma.

Divisions:	*1.*	*2.*	*3.*	*4.*	*5.*	*6.*	*7.*
	Control mice tarred, then bred.	*Divisions 2, 3, 4, 5 and 6 were bred untarred.*					*Control mice tarred, then bred.*
Diet	*C.D.*	*C.D.*	*S.D.*	*S.D.*	*NHVC*	*NLVC*	*NLVC*
1st Gen.	Jan. 1/37 Feb. 12/37	July 16/36	July 6/36	July 6/36	July 6/36	July 16/36	Jan. 17/37 Jan. 21/37
2nd Gen.		Jan. 1/37 Jan. 3/37 Jan. 6/37	Sept. 7/36 Litter 10	Sept. 12/36 Litter 10	Sept. 24/36	Nov. 11/36	
3rd Gen.			Dec. 1/36 Dec. 7/36	Nov. 29/36	Dec. 25/36 Jan. 7/37	Jan. 20/37 Jan. 24/37	
4th Gen.			Feb. 3/37 Feb. 6/37	Feb. 13/37 Feb. 16/37			
	1st Gen.	2nd Gen.	4th Gen.	4th Gen.	3rd Gen.	3rd Gen.	1st Gen.
	The mice in the last generation of each division were divided into two groups, group (a) and group (b). Group (a) was placed on the low vitamin content (control diet), and group (b) on the high vitamin content diet, Table III.						
Gr. (*a*)	8 M	7 F	6 F	6 M	7 F	7 F	6 M
Gr. (*b*)	3 M 4 F	8 F	6 M	8 F	6 M	7 M	7 F

M = Male. F = Female. Gr. = Group. C.D. = Control diet. S.D. = Control diet with vitamin content increased by one-half. NHVC = Milk, lettuce, wheat germ cereal, whole wheat bread and lard. NLVC = Milk, carrots, oat-chop, white bread and lard.

All mice of this series received milk once a day (morning) and water at night.

TABLE III.

The mice in the last generation of each division in Table II were divided into two groups, group (*a*) and group (*b*). Group (*a*) was placed on the low vitamin content (control diet), and group (*b*) on the high vitamin content diet.

Group	*Age (months)*	*Number of mice*	*Diet*	*Tarrings*	*Remaining mice*	*Growths for biopsy*		*Days after L.T.*	*Histological report for carcinoma*	*Remaining mice*
					May 28	*May 28*	*June 28*			
Gr. (*a*) Div. 1	2-2½	8 M	C.D.	27	4	4	..	13	4	3
Gr. (*b*) Div. 1	2-2½	7 {3 M, 4 F}	HVC.	27	7	..	1	20	1	6
Gr. (*a*) Div. 2	2-2½	7 F	C.D.	27	7	..	4	20	4	7
Gr. (*b*) Div. 2	2-2½	8 F	HVC.	27	8	..	1	20	1	8
Gr. (*a*) Div. 3	2-2½	6 F	C.D.	27	6	..	2	20	2	6
Gr. (*b*) Div. 3	2-2½	6 M	HVC.	27	4	..	0	20	0	4
Gr. (*a*) Div. 4	2-2½	6 M	C.D.	27	6	..	1	20	1	6
Gr. (*b*) Div. 4	2-2½	8 F	HVC.	27	7	..	1	20	1	7
Gr. (*a*) Div. 5	2-2½	7 F	C.D.	27	7	..	0	20	0	7
Gr. (*b*) Div. 5	2-2½	6 M	HVC.	27	4	..	0	20	0	4
Gr. (*a*) Div. 6	2-2½	7 F	C.D.	27	7	..	0	20	0	7
Gr. (*b*) Div. 6	2-2½	7 M	HVC.	27	5	..	0	20	0	5
Gr. (*a*) Div. 7	2-2½	6 M	C.D.	27	6	5	..	13	5	6
Gr. (*b*) Div. 7	2-2½	7 F	HVC.	27	7	..	1	20	1	7

M = Male. F = Female. Gr. = Group. Div. = Division. L.T. = Last tarring. C.D. = Control diet. HVC. = High vitamin content diet.

Figure 1 shows the present condition of the remaining mice.

bination of vitamins with increased dosage was essential to maintain normal reproduction, and that when the dosage of vitamins was increased tumour growths among mice under treatment appeared much less frequently. These findings, together with a working knowledge of the amount of tar-irritation required for this particular strain of mice and of the part played by diet and reproduction in the resistance of the animal to tumour growth (or, as one might term it, "malignant tumour threshold"), determined the dosage of vitamins for the two diets used in this series (Table III).

The control diet produces a normal, healthy mouse. If the mice are bred untarred, it has a slight tendency to raise the tumour threshold (group (*a*) division 2), or when the tumour threshold is raised (group (*a*), divisions 3, 4, 5 and 6), few if any tumour growths appear on this control diet, indicating that the standard of the tumour threshold can be modified. When it was reduced or maintained at a lower standard through treatment, as in the parents of the control mice of this series, this diet will not protect the animal from cancerous growths (group (*a*), division 1 and group (*a*), division 7), so that the dosage of vitamins in the diet has to be increased in proportion to the amount of treatment given or the tumour threshold standard the animal possesses at the beginning.

Comparing the divided control litters on the control *vs.* the higher vitamin diet (group (*a*), division 1 *vs.* group (*b*), division 1, and group (*a*), division 7 *vs.* group (*b*), division 7), Table III records the number of growths and histological findings, while Fig. 1 shows the present condition of the mice in the two groups on the two different vitamin diets. This method of comparison may be applied to all the other groups, taking into consideration the background of the mice in the different groups.

CLINICAL BEHAVIOUR OF TUMOURS PRODUCED BY TAR-IRRITATION IN MICE ON DIETS WITH VARYING DOSAGES OF VITAMINS

Growths that appear in mice on the higher vitamin diets usually resemble warty growths with little or no thickening of tissue at the base attachment, and are unlike those found in mice on the lower vitamin diets, in which the growths usually have a thickened indurated base. Some growths later seem to become quiescent, and remain so; others become dark on the surface and later disappear. Mice, anxious to have the growth removed, keep up a constant irritation by scratching, and other mice in the group sometimes assist in removing the growth with their teeth. *If the surrounding tissue becomes damaged, infection of the growth is quite common among mice on the lower vitamin diets, and is rarely found among those on the higher vitamin diets.*

Growths appearing in the early part of this experiment almost always progressed to carcinoma (Table I). Of the few growths which have appeared (outside of the control groups) in this series, in from two to six weeks after cessation of treatment, some have since disappeared, others have become quiescent, clinically resembling small warty growths. This applies also to the mice where growths have been removed for biopsy and have shown carcinoma (Fig. 1, group (*a*), division 2). One mouse in group (*a*), division 6, has recently developed a growth which may be of a cancerous nature, on the right side in a part untreated, and which is at present progressing slowly. On the termination of treatment the tumour threshold standard of this group may have been close to the lower border line level, as these mice were on one of the poorest diets throughout this experimental series until treatment began. It is interesting to compare this group (*a*), division 6, with the control groups (group (*a*), division 1, and group (*a*), division 7), on the same low vitamin diet. The control groups at biopsy May 28, 1937, all showed carcinoma, with the exception of one mouse, and this one has since developed a growth. Also compare this group with its fellow mates, (group (*b*), division 6), which were on the higher vitamin diet and all free from growths. Similar comparisons may be made in different ways among the mice in the other groups.

On placing a few mice that had been on a low vitamin diet and had well developed tumour growths on a diet with vitamins A, B and E greatly increased, the smaller growths became dark on the surface and the indurated tissue at the base of the hyperkeratosis type of growth became soft and easily detached, leaving a raw surface with an apparent attempt at healing at the surrounding edges. This observation requires further study.

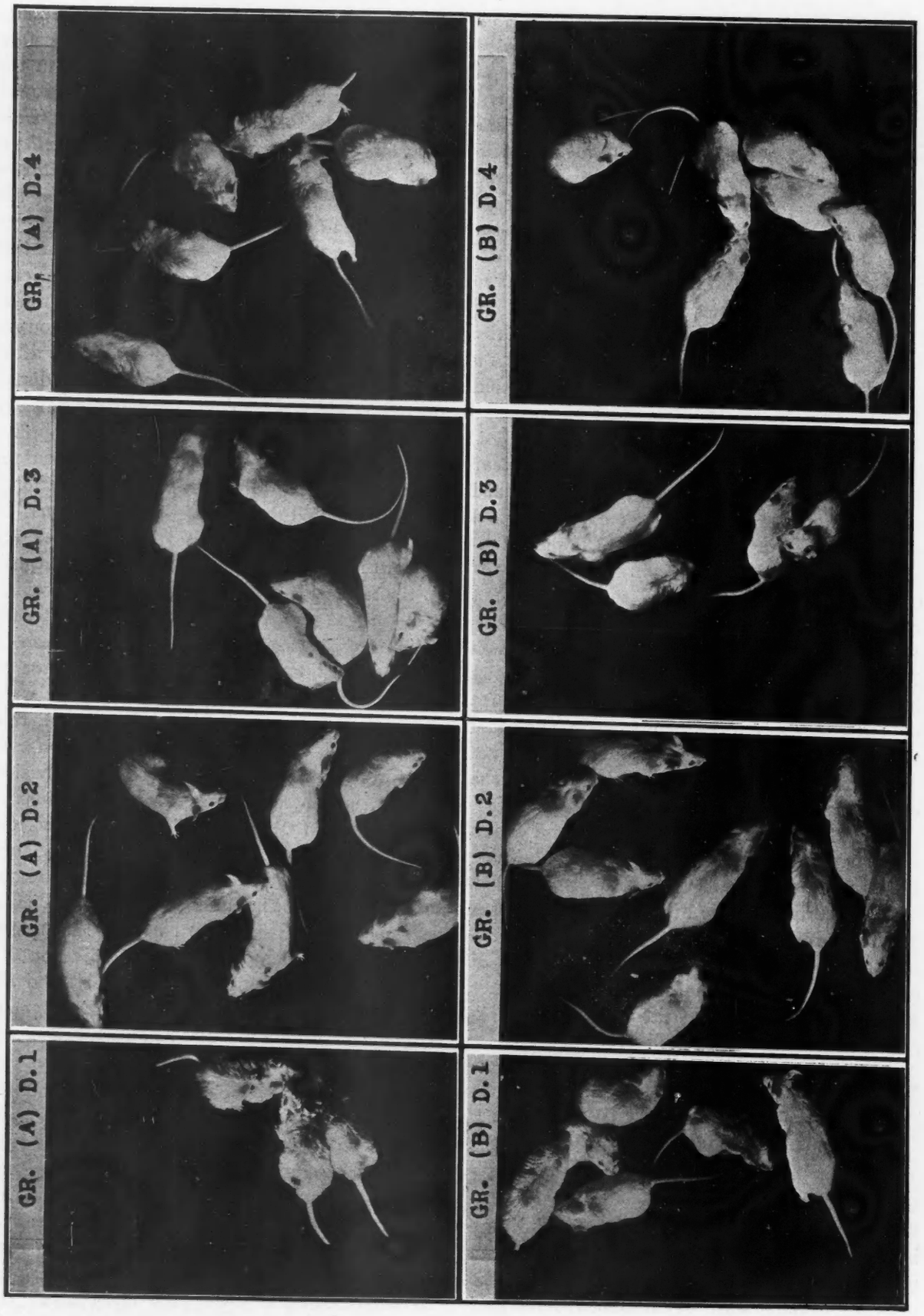
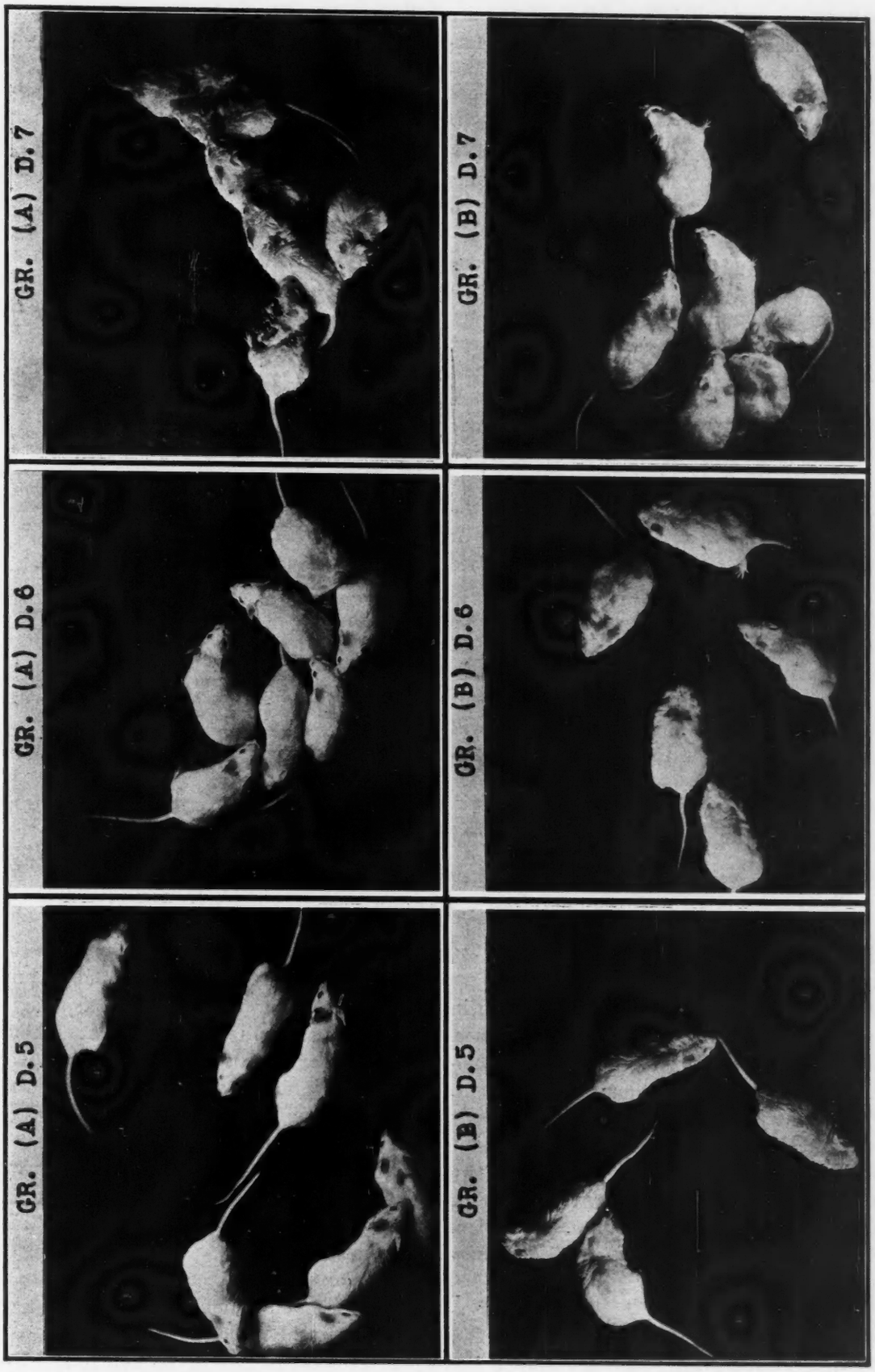


Figure 1


GR. (A) D.7
GR. (B) D.7
GR. (A) D.6
GR. (B) D.6
GR. (A) D.5
GR. (B) D.5

SUMMARY

After observing for six years over 600 mice under treatment to produce and inhibit tar-carcinoma it seems to be fairly well demonstrated that the tumour threshold of the mouse can be lowered by tar-irritation, and raised or maintained at a fairly constant level by breeding and diet, with varying dosages of vitamins administered in the diet (especially those associated with reproduction, A, B and E).

At the present stage of this experiment one observes a distinct difference in the condition of the control groups on the two different vitamin diets. Fig. 1 represents the present condition of the mice in this series at an average age of 253 days. If one wishes to get a greater contrast one could increase the dosage spread of vitamins in the diets at the expense of the vitamins in the control diet.

A year or more will probably pass before the mice in this series die, as all but one, outside of the control mice on the low vitamin diet, are at present returning to normal health.

The following information obtainable with the completion of this series, on the death of all the experimental mice, will be of help in adjusting vitamin dosage: (1) whether the present vitamin dosage of the high vitamin diet will maintain the animal throughout life or will have to be increased with age, and (2) to observe the tumour threshold in groups (*a*), 2, 3, 4, 5 and 6, that have been on control diet with low vitamin content.

Though these experiments deal with a comparatively small number of mice, this article is now offered for publication in order that the procedure and findings may be of service to those interested, who have the time, place and financial means to further the work.

I desire to acknowledge the assistance given by the following, which made this research possible: Dr. Sarah Meltzer, Assistant Pathologist of the Winnipeg General Hospital, for carrying out the histological examination of the growths and pathological work; Council of College of Physicians and Surgeons of Manitoba, for granting the Gordon Bell Memorial Fund 1934-35, $900.00; 1935-36, $900.00; 1936-37, $525.00; Mr. Geo. McLean, G. McLean Co. Ltd. (wholesale grocers), $1,000.00; Dr. Fred Cadham, Provincial Bacteriologist, for donating some mice at the beginning of the experiment; Dr. W. F. Geddes, Grain Research Laboratories, Winnipeg, for supplying some wheat germ oil in the beginning of the experiment, when it was difficult to obtain; Mr. A. W. Alcock, Western Canada Flour Mills, for supplying wheat germ cereal; Mr. W. G. Bower, representative of Ayerst, McKenna & Harrison, for supplying some cod liver oil.

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THE IMMEDIATE TREATMENT OF FACIAL FRACTURES

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INCREASED speed of modern vehicular traffic, plus the widespread adoption of its use, have resulted, among other things, in an increase in the number of accidents involving the face. Fractures of the facial bones, no longer uncommon, require careful and thorough treatment. Here, as in all fractures, the functional result is important, but in addition the cosmetic result has to be considered. There are therefore two important fundamentals in the treatment of facial fractures, *viz.*, the restoration of function, and the minimizing or prevention of disfigurement.

THE MALAR BONE

Fractures of the malar bone are always the result of direct violence. The diagnosis is usually easy. Following an injury swelling appears in the affected region. Subconjunctival hæmorrhage may be present. Other signs and symptoms are unilateral epistaxis, numbness in the maxillary teeth and the upper lip on the injured side, inability to fully open the mouth, and occasionally a lowering of the eye on the side of the injury. The latter sign may cause diplopia. Palpation of the bony orbit in such cases will commonly reveal a break in the normally smooth contour. This may be at the external angular process, or at the point where the malar joins the maxilla. Here, as in all fractures, confirmation of the clinical diagnosis is to be sought radiologically.

Treatment consists in the replacement of the loose fragment. In the vast majority of cases

the piece once replaced remains so. Even slight displacements of the malar-zygomatic compound should be restored to normal position, since even these, untreated, may result in a rather disfiguring flattening of the side of the face.

Many methods are advocated for the treatment of malar fractures. That devised by Gillies is, in our experience, both satisfactory and safe. Under general anæsthesia a short longitudinal incision is made in front of and above the ear on the injured side, the hair having previously been removed. This incision is carried down to the temporal fascia. The fascia is split in the direction of its fibres and an elevator passed deep to it. As this fascia is attached below to the malar-zygomatic compound the instrument must pass deep to the loose fragment. Force is now applied in the proper direction to return the detached bone to its normal position (Fig. 1). The fascia and skin are then closed. Gillies' method has distinct advantages. The incision is well away from injured or infected areas; no important structure can be injured; the necessary force can be applied easily; and the scar is small and well hidden.

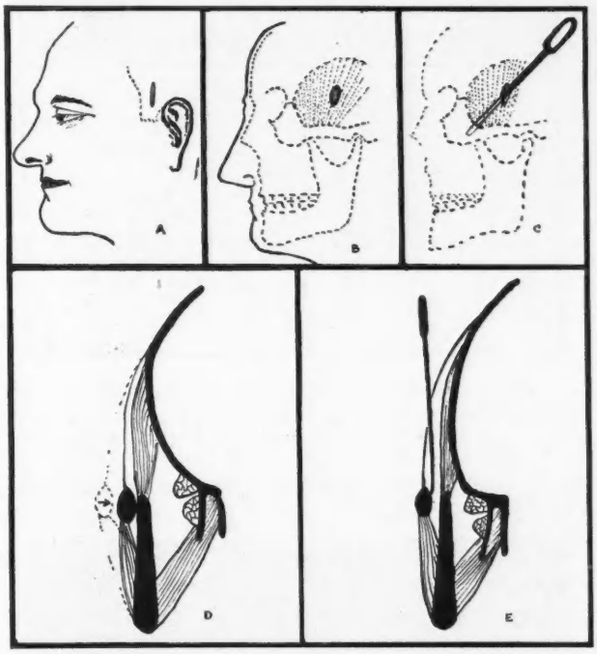

Fig. 1 illustrates the steps in the reduction of a fractured malar.

A. The location of the incision is shown well within the hair-line.
B. Illustrates the corresponding incision in the temporal fascia.
C. Shows the elevator introduced deep to the temporal fascia and malar-zygomatic compound.
D. Diagrammatic representation of a coronal section through the ascending ramus of the mandible. The malar bone is represented as being driven in and lying against the coronoid process of the mandible.
E. Shows the level at which the elevator is passed and the reduction of the malar bone to its normal position.

NASAL FRACTURES

Fractures of the nasal bones offer no very great difficulties in diagnosis. Inspection alone is usually sufficient. All nasal fractures are the result of direct violence. The nose is either collapsed upon itself or pushed to one or the other side. Reduction is done under general anæsthesia. Using some suitable type of forceps, *e.g.*, Walsham's, the nose is moulded into shape. Here again the tendency is for the replaced fragments to remain in position (Fig. 2). Occasionally the fractured nose will not retain its corrected position. For this type of case we have used satisfactorily the Straith splint. Any splint used in the treatment of nasal fractures must be watched very carefully to prevent ulceration due to pressure.

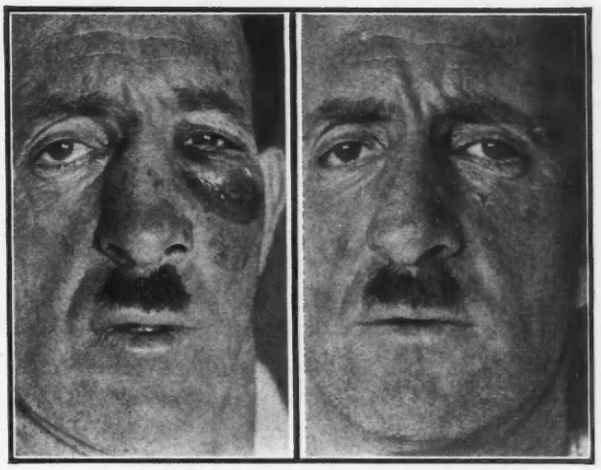

Fig. 2.—Fracture of the nose. The result obtained by simple moulding with forceps is shown.

THE MAXILLA

The maxilla, in our experience, is fractured more rarely than any other facial bone. Direct violence accounts for all such fractures. The position and extent of the fracture depend on the degree and direction of the violence.

Fractures of the alveolar ridge can be managed usually by interdental wiring. Bilateral horizontal fractures of the maxilla can be treated in one of several ways. A metal cap splint may be fastened to the upper teeth and bars led from it out to the angles of the mouth and back over the cheek, these bars in turn

being fastened to a plaster head piece; the antra of Highmore may be packed, with later interdental wiring; or the upper teeth may be fixed to a jury-mast attached to a head-piece of plaster. The last method is dependable and simple. Under light anæsthesia, *e.g.*, avertin, the maxilla is manipulated into normal position. This position can be checked by bringing the mandibular teeth into relation with the maxillary and noting the occlusion. A band of heavy silver (or brass) wire is fastened to the upper teeth with several ties of fine wire (brass: stainless steel), and this band in turn fixed from two

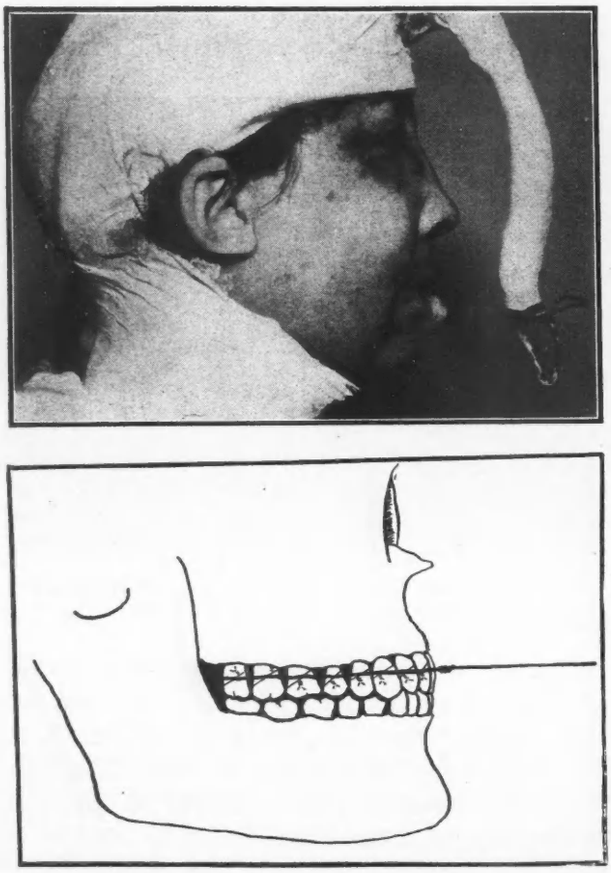

Fig. 3.—This illustrates the type of apparatus used for maintaining fractures of the maxilla after reduction.

points to a jury-mast extending from a head plaster downwards in front of the face (Fig. 3). Fixation should be maintained for four to five weeks.

THE MANDIBLE

Mandibular fractures are common. They result from direct or indirect violence. Occasionally they are pathological. In many cases the fracture is bilateral, through the area of the mental foramen on one side, and in the region of the angle on the other. Practically all fractures of the body of the mandible are compound into the mouth. Diagnosis is not difficult as a rule. The history of injury, localized pain, deformity, and abnormal movement are practically always definite.

A thorough cleansing of the mouth should precede splinting. Early reduction and fixation lessen the chance of infection. It is wise to remove a tooth in the line of fracture. Its presence invites infection, and while occasionally it may be left with safety, as a general rule it should be sacrificed.

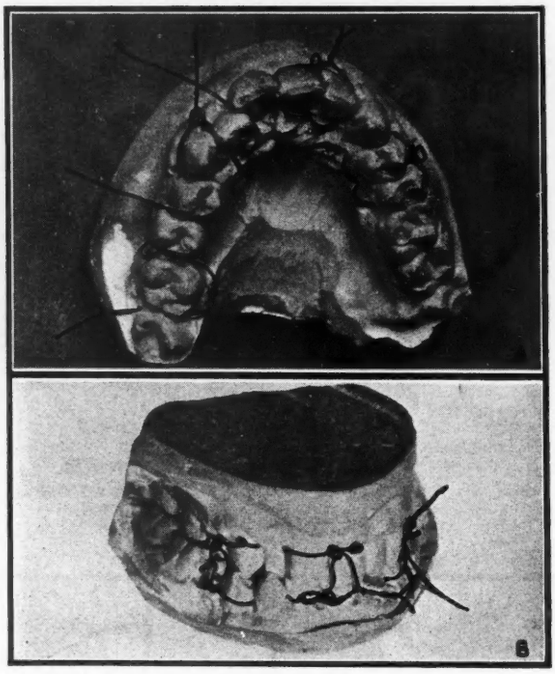

Fig. 4.—This illustrates Ivy's method of applying tie wires in fractures of the mandible.
A. Illustrates the various steps in fastening the wire to each set of teeth.
B. Illustrates the fastening of the upper and lower sets of wires together.

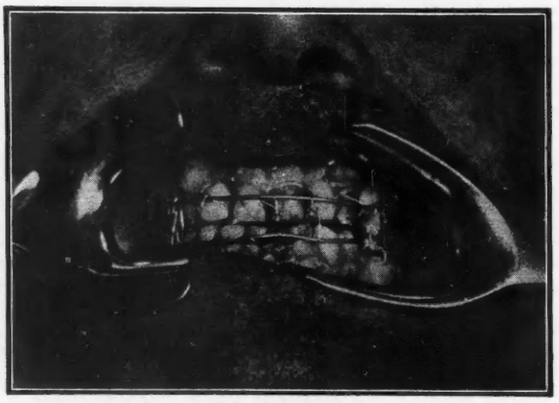

Fig. 5.—The band wire method of fastening is illustrated. The band wires are of silver, the tie wires of stainless steel.

Fractures of the mandible are best treated by bringing the mandibular teeth into proper relation with the maxillary teeth and fastening them there. This should be done if possible without an anæsthetic or, failing this, with an inferior dental nerve block. If the teeth are of the proper shape to hold tie wires applied after the manner of Ivy (Fig. 4) then such ties are applied. The teeth usually fastened are the right and left bicuspids and the central incisors. If the teeth are so placed or shaped that such ties are not feasible heavy band wires are fastened to the upper and lower teeth (Fig. 5). The two band wires are then fastened together. Brass or stainless steel wire may be used as ties.

Once the upper and lower teeth are fastened together, the frequent use of a mouth wash is essential. Our preference is for a 1-10 solution of hygeol. The patient must take constant care of his teeth during the period of splinting. Food, of course, must be fluid, or, at most, semi-fluid. It may be given through a nasal catheter if necessary. Ordinarily patients will get sufficient through a suction tube.

Splinting is maintained for five weeks. A further two weeks of care in regard to diet is advisable, only soft foods being taken during this time.

CONCLUSION

The methods of treatment outlined above have the virtue of simplicity. No attempt has been made to detail treatment for the more complicated fractures of the mandible and maxilla.

OSTEOMYELITIS OF THE SUPERIOR MAXILLA IN NEW-BORN INFANTS*

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OSTEOMYELITIS of the maxilla in new-born infants is a condition which, though comparatively rare, deserves more prominence than has been accorded to it in a somewhat scanty literature on the subject. It presents a strikingly uniform clinical picture of fever, swelling of the cheek and eyelids on the affected side, suppuration pointing both on the cheek and inside the mouth, unilateral nasal discharge, augmented by pressure on the cheek, and finally sequestration of one or all surfaces of the maxilla, with loss of deciduous teeth and permanent tooth buds, and often deformity of the affected side of the face. It is now generally believed that cases reported in the early literature[1] as empyema of the antrum of Highmore in new-born infants were all cases of the condition under discussion.

The first case of osteomyelitis of the superior maxilla reported in the English literature was by Douglas[2] in 1898, and in the American literature by Posey in 1912.[3] Wilensky[4] in a recent publication gives a comprehensive review of the clinical course, pathogenesis and treatment of the disease. He states that the *Staph. aureus* is the commonest organism found. It is his impression that the available sources of the infecting organisms are: (1) the vaginal canal of the mother; (2) the fingers of the accoucheur or of the nurse; (3) the nipples and breasts of the mother, and (4) the fingers or apparatus used in cleansing the baby's mouth after birth. Various discussions have centred on the method and the point of entry of the organisms into the maxilla and from whence they come. The majority of observers favour a primary lesion. The infection having once entered in the maxilla, the bacteria develop further in the spongiosum of the bone. Poncher and Blayney[5] believe that the part played by nasal infection and sinusitis (maxillary and ethmoid) is more important than is commonly believed. The histological study of their case corroborates that statement.

The general clinical course presents a clear-cut, definite picture, one case report being very much similar to another. The disease usually affects healthy infants between two and ten weeks of age. There is a short prodromal period, after which clinical manifestations of a severe infection are evident. There is high

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fever, and the infant appears extremely ill. A swelling appears either in the cheek or in the infra-orbital region, and is usually accompanied by œdema of the lower eyelid. Sometimes there is exophthalmos from œdema of the orbit. The sclera is inflamed, conjunctivitis is present, and sometimes there is chemosis. In the majority of cases localization occurs below the inner canthus of the eye. At this site a swelling in the cheek appears, with redness, abscess formation, the breaking through of pus, and the formation of a fistula. In the mouth can be noticed swelling of the alveolar process and of the hard palate, followed by perforation, the discharge of pus and the formation of a fistula. Another common and characteristic symptom is the discharge of premature teeth through the alveolar sinuses. In nearly all cases, there is sooner or later a discharge of pus from the nose, which is increased by pressure on the abscess. All of these changes occur within a few days. The majority of children are seriously ill, but a few remain surprisingly well in spite of the progress of the disease. The outcome is either death within a day or two of onset or healing, with or without the persistence of discharging sinuses, or the development of secondary purulent foci.

The local manifestations correspond to those of a sequestrum in an abscess of larger or smaller extent. The characteristic phenomenon of exfoliation of teeth or tooth buds should by itself suffice to call one's attention to the correct condition. The final result if the child lives, is a considerable deformity of the face and palate, with loss of teeth, both temporary and permanent, on the side involved.

The details of our case are as follows.

K.K., a white male, three weeks old, weighing seven pounds, was admitted to the Jewish General Hospital on January 30, 1937, with the following history.

He was born at term. The delivery was not difficult; low forceps were used at the end of the second stage. The birth weight was seven pounds, one ounce. The mother was thought to be suffering from tuberculosis, but the diagnosis has never been corroborated. Nothing remarkable occurred during his stay in the hospital, and the patient was discharged at two weeks of age weighing seven pounds, three ounces.

On the day following discharge the infant developed a temperature of 101° and a swelling of the right eye. The temperature remained elevated for several days, and the baby was seen several times by the family physician. He was thought to have had erysipelas. He was then seen in consultation by one of us (A.G.), when it was found that on examining the mouth the entire superior alveolar margin on the same side presented a soft fluctuating swelling, which on incision yielded a great quantity of pus apparently coming from the region of the superior maxilla. The child had two small superficial abscesses, one on the left cheek and one on the left leg, both of which were incised and yielded abundant pus. The child was admitted to the Jewish General Hospital with a diagnosis of osteomyelitis of the right maxilla and pyæmia.

On admission to the hospital the swelling of the face was gone, but a fluctuating abscess was present in the left forearm immediately below the elbow joint. This was incised. Purulent material was obtained and the tension was released. Culture of the pus gave a growth of a non-hæmolytic staphylococcus. A course of staphylococcus toxoid was begun on the same day and the abscess began to heal.

The following day, January 31, 1937, the right side of the face again became swollen and the eyelids were so œdematous that the right eye was closed. Intraorally, the upper gum in the region of the premolar tooth exuded pus and the adjacent cheek appeared white. The temperature was normal at this time, and the abscess of the arm drained well. On February 2, 1937, a unilateral purulent nasal discharge was noted from the right side. This confirmed the diagnosis of osteomyelitis of the right maxilla. The patient was seen by Dr. A. O. Freedman, oto-laryngologist, on February 5, 1937, who made the following note "There is a boggy mass over the region of the anterior wall of the right antrum. There is a cellu-

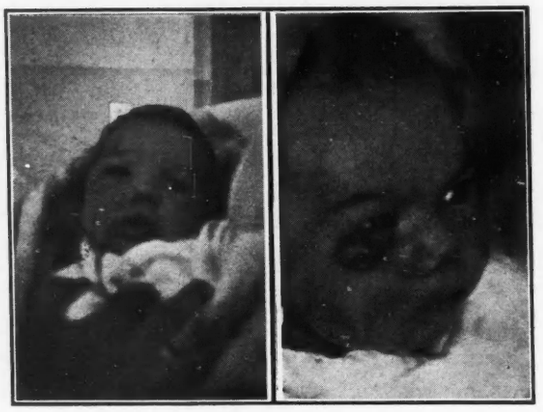

Fig. 1 Fig. 2

Fig. 1.—Appearance of patient three days after admission, *i.e.*, February 2, 1937—with typical appearance of osteomyelitis of the right maxilla. Note pus coming from the right nostril.

Fig. 2.—Appearance of patient on March 15, 1937, with a complicating infra-orbital abscess.

litis of the lower right eyelid in the region of the right pre-molar tooth. There is a sinus leading into the antral mass. Pus exuded through this sinus." X-ray of the skull on that day showed no definite evidence of bone involvement; however definite crepitus of the malar bone was elicited by palpation.

Operation was performed on the same day and the operator's report read: "On lifting up the upper right lip a fistulous opening was seen in the midline of the alveolar process of the right upper maxilla. (This was the result of a previous incision.) An incision was made over the maxillary process from the region of the incisor laterally towards the tuberosity of the maxilla. A free rush of pus resulted. On elevating the cheek from the underlying bare bone a mass was encountered. On gentle manipulation it was found that this bony mass was rather loose, consisting

of probably the upper maxilla and the malar bone. The cavity was aspirated. A piece of packing was inserted inside this cavity. The right nostril was filled with pus, and this was aspirated.

At this time the blood picture was erythrocytes, 3,050,000; leucocytes, 17,500; Hgb., 64 per cent; polymorphonuclears, 64 per cent; stabs, 7 per cent; lymphocytes, 20 per cent; eosinophiles, 9 per cent, and because of the anæmia and poor general state a small blood transfusion was given.

Following drainage of the antral empyema, the child's condition improved and the swelling of the face subsided. A roentgenogram, 10 days after operation, showed a destructive process of the right malar bone. During the intervening period the child was taking feedings well and showed marked improvement. Suction was applied daily to the open antral wound, to encourage drainage of pus. Further roentgenological examination on March 15, 1937, revealed erosion of the right maxillary region with the formation of a bony sequestrum. With this erosion, the right side of the face became quite flattened. One month following the primary antral operation a secondary operation was performed, at which time bony sequestra were removed through the antral wound, and the area of drainage enlarged. Following this a swelling developed over the right eye, which became reddened and fluctuant and was incised and drained by Dr. H. Ballon. Following incision of this infra-orbital abscess there was an unduly long period of drainage, with spontaneous discharge of purulent material, best explained by the presence of a sinus leading into the antral area. The temperature remained normal throughout all this, and the drainage over the right eye eventually subsided and ceased entirely. On April 12, 1937, another operation was performed and more sequestra were removed from the antral region and better drainage instituted. All purulent material was cultured and yielded a growth of non-hæmolytic staphylococci. The blood culture was negative.

The child's general nutritional state was good, and he continued to gain weight, weighing twelve pounds on discharge. The Mantoux test was negative. The examination of the urine showed nothing abnormal. The blood Wassermann test was negative.

Because of the long period of convalescence necessary it was decided to send the child home on April 19, 1937, under the mother's care, with periodic supervision of the local lesion by the physician in charge.

The diagnosis was: osteomyelitis of the right maxilla; right antral empyema; infra-orbital abscess; abscess of the left arm; secondary anæmia.

This case is reported to call attention to a condition which manifests classical signs so typical that one case is almost an exact replica of any other. Any new-born infant presenting a unilateral swelling of the face with fever, should be suspected of suffering from this condition. When the unilateral nasal discharge develops in addition the diagnosis is complete. The prognosis is usually good; children surviving the first onslaught of the infection usually recover, although the convalescence may be greatly prolonged and complicated by frequent sequestrations of dental buds or bits of the maxillary bone.

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ATROPHIC RHINITIS: THE CONSTITUTIONAL FACTOR: AND THE TREATMENT WITH ŒSTROGENIC HORMONES*

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IN this disease of the human nose, which has been known since antiquity, at least eight theories have been advanced in explanation of its etiology.[1] Although it is apparently a local pathological condition, it has for long been known to affect females more frequently than males, and more often to affect certain families and stocks. Therefore the general conclusion is that there is present, in those liable to suffer from it, a constitutional factor which makes the pathological condition possible. It has, however, been hard to reconcile the occurrence of a disease, so relatively localized in its site, with an etiology dependent upon a constitutional nature or diathesis, since constitutional states are apt to produce widespread rather than local disabilities. Despite the fact that of recent years the literature on this disease shows evidence of an increasing recognition of the importance of this undefined constitutional predisposing factor, there has so far been lacking an adequate explanation of the mode by which a familial constitutional condition may affect the localized area which becomes the site of the disease.

Speculation as to the possible links in the

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etiological chain gave rise to the presumption that a susceptible individual was born with a predisposition to a pathologico-anatomical abnormality of the facial part of the skull in growth, of the order of chamæprosopia, a component part of which was the acquisition of abnormal nasal width. It was also necessary to have an exciting factor. It was suggested that this might be such local infection as sinusitis, or such general disease in childhood as diphtheria, scarlet fever, etc.; these supposedly leading to degeneration of the sphenopalatine ganglion, which, by neurotrophic influence, led to mucosal atrophy. In the absence of such exciting causes it was suggested that defective development of the nose might in some way also involve the ganglion, which would thus come to have an "inherent lack of resistance".[2]

Our interest in this problem arises from the clinical demonstration[3] of the frequency of occurrence of cranial dysplasia, acquired both during and after the growth period, in patients who later in life were shown by careful physiological investigation to suffer from disturbance of function of the anterior lobe of the hypophysis; and by the experimental demonstration in this laboratory of the influence of pituitary and associated hormones on the animal cranium.[4]

TABLE I.

CRANIAL DYSPLASIA IN ATROPHIC RHINITIS

TYPE—AGE DISTRIBUTION

	Males		*Females*	
Youngest case...	9 years		6 years	
Oldest case.....	59 years		66 years	
	Cases	*Average age*	*Cases*	*Average age*
Normal Crania....	4	16.5 yrs.	3	16 yrs.
Dysplasia Type I	7	24.8 "	4	21.2 "
" " II	2	31.5 "	5	36.4 "
" " III	8	14.5 "	7	12.8 "
" " IV	3	32.3 "	19	31.1 "
" " V	0	...	6	31.1 "
Total.....	24	(21.1)	44*	(28.6)
	35% of Series.		65% of Series.	

Ozæna present in 12 cases (50% of males); 28 cases (62.2% of females). 58% of Series.
*Female Case 41 was not x-rayed.

Some idea of the relative frequency of atrophic rhinitis and ozæna in a general population today is to be obtained from the fact that, over a period of almost 2½ years, in the Department of Oto-Laryngology in the Montreal General Hospital, 69 patients suffering from this condition have been found. The majority of these are adults or adolescents, the average age of the group being 25 years. It is, of course, a small series, a fact which has to be kept in mind in estimating the value of any trends that may appear in a statistical presentation of the material.

In this series 65 per cent were females (45 cases) and 35 per cent males (24 cases) (Table I). In the males the youngest was 9 and the oldest 59 years of age; in the females the youngest was 6 and the oldest 66 years old; 58 per cent of the group showed ozæna, non-fœtid atrophic rhinitis being somewhat less frequent. Ozæna, however, was (not significantly) more frequent in the females, being present in 62.2 per cent, (28 cases) against an occurrence of 50 per cent in males (12 cases). Parenthetically, it may be said that the oto-laryngological staff of the General Hospital regards atrophic rhinitis and ozæna as essentially the same pathological entity, the latter being the more severe form.

That the condition in both its forms affects females significantly more than males, and predominantly occurs in association with the growth period and earlier adult life can be seen from Chart 1, in which the cases are arranged in both sexes according to the frequency of occurrence from the first to the fifth decades of life. Although the numbers are too small to form a reliable basis of judgment beyond the third decade, it is felt that a trend may be indicated. The condition is most frequent in the second decade of life in both sexes; somewhat more than half the cases show ozæna; and females are more frequently affected than males. This disparity between the sexes, not only as regards the numbers affected but in the relative frequency of ozæna in the two sexes is more clearly apparent in the second and third decades. In the first decade the female cases are one fewer

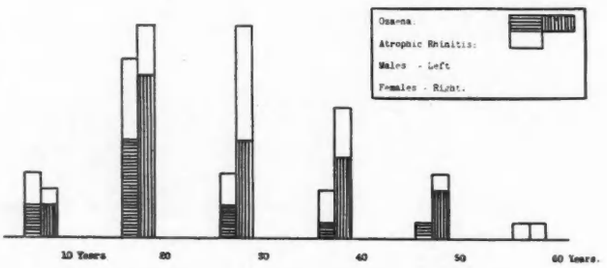

Chart 1.—Ozæna and atrophic rhinitis by decades.

than the male, but the total number is too small to put any stress on this. The chart, however, would seem to bear out facts which already have been noted by other observers, dealing with larger series, namely, that the disease most frequently appears (or is most frequently seen) about puberty, roughly, in the second decade. It also supports the statement of other observers, such as Adam,[5] who found that 42 per cent of his cases occurred in the first 7 years of life, that more careful or earlier investigation would reveal that the condition, which is not congenital, frequently begins in the first decade, and that it is only after it has lasted some time and made considerable progress that the patient seeks advice or is brought by a parent for treatment, for which reason it has been held that the disease usually appears in the following (second) decade.

The conjecture that the disease is in some way related to sex, in that women are at all ages more frequently affected than men, would appear to be borne out in this small group, further strength being lent to this conjecture by males and females being most affected both with atrophic rhinitis and ozæna in the second decade. Of course it may be argued that women are more apt to seek advice than men for a disease which causes personal embarrassment; and that in both males and females a personal defect, which may be a source of offence to others, is more apt to lead to dissatisfaction and inferiority feeling in the adolescent and post-adolescent period, when self-consciousness is greater than either earlier or later in life.

TABLE II.

CRANIAL DYSPLASIA IN ATROPHIC RHINITIS

TYPE—SEX DISTRIBUTION

	Males *Per cent*			*Females* *Per cent*		
Normal Crania...	16.6			6.8		
Dysplasia Type I	29.2	37.6%	54.2%	9.1	20.5%	84.1%
" " II	8.4			11.4		
" " III	33.3			15.9		
" " IV	12.5	45.8%		43.2	72.7%	
" " V	0			13.6		

Types II, IV and V are characterized by calvarial sclerosis, which is seen to occur *three* times more frequently in the female cases (males 20.9%, females 68.2%).

Lateral and postero-anterior cranial skiagrams were taken of all but one case, a penetrometer being used.[3] Examination of these revealed the following facts (Table II). Of the 44 females only 6.8 per cent showed normal crania. Of the remainder, 20.5 per cent, as judged from the cranial skiagram, manifested overactivity of the anterior pituitary during the growth period, and of these 11.4 per cent had subsequently suffered a stage of pituitary hypofunction, indicated by the fact that sclerosis had occurred in the calvaria (Table III).

TABLE III.

CRANIAL DYSPLASIAS OF PITUITARY ORIGIN

(MORTIMER, LEVENE AND ROWE)

Dysplasia Type	I	*Cancellous hyperplasia* in brain-case and face: Diploic "expansion". Hyperplastic paranasal sinuses. Prognathism (?). Progeniacism (?).
"	" II	An earlier Type I change plus secondary calvarial *sclerosis.*
"	" III	*Cancellous hypoplasia* of brain case and face: Hypoplastic diploe. Hypoplastic paranasal sinuses. Progeniacism (?).
"	" IV	An earlier Type III change (usually of moderate degree) plus secondary calvarial *sclerosis.*
"	" V	Normal proportions in brain-case and face plus secondary calvarial *sclerosis.*

The remaining females (72.7 per cent) showed evidence of definite hypopituitarism during growth, when 15.9 per cent, with an average age of 12.8 years (Table I), showed a type III dysplasia. Even a larger number, 43.2 per cent, the largest single group in the female dysplastic series, showed type IV dysplasia, which, as we have already said, indicates, by the calvarial sclerosis, engrafted upon an earlier type III change, a continuing hypopituitarism. Their average age is 31.1 years, which would seem to indicate that such sclerosis appeared to take about 20 years of hypopituitarism to produce.

The remainder, 13.6 per cent, showed type V dysplasia, indicating a hypopituitarism occurring after the brain-case and face were fully differentiated. The average age was 31.1 years, and if we consider the female calvaria to be fully differentiated at 20 years, then the sclerosis, which in such cases is the only cranial evidence of hypopituitarism, has had on the average 11 years' duration. Finally, in the female cases, if we group all those which at one time or another show, in cranial proportion or structure, evidence of hypopituitarism, we find

that 84.1 per cent of the total are accounted for.

In the group of 24 males, 16.6 per cent had approximately normal crania. Of the remainder, 37.6 per cent had during the growth period shown evidence of pituitary overactivity, although a small number of these (8.4 per cent) did give evidence of later glandular underactivity. Of the males 45.8 per cent showed consistent hypopituitarism; 33.3 per cent of them, averaging 14.5 years, were hypopituitary during the period of active growth (Table I), and 12.5 per cent, with an average age of 32.3 years, showed hypofunction both during and after the growth period by a calvarial sclerosis which appeared to take almost 18 years to produce. If, similarly, we consider the male cases of dysplasia, grouping together all which at one time or another have shown any evidence of hypopituitarism, we can account for half of their number (54.2 per cent).

If, for a moment, we regard the complete group of patients, males and females, in the light of a special physiological constitution indicated by cranial skiagrams, disregarding for the moment the fact that they have the common characteristic of a nasal disease, and giving our attention to only one feature in their crania, namely, the calvarial sclerosis which characterizes types II, IV and V dysplasia, we obtain confirmation in this group of a characteristic which we have already established in two other groups of dyspituitary crania. We find that sclerosis is present three times more frequently in the female cases than in the male (females 68.2 per cent; males 20.9 per cent). In an earlier series of 494 dysplastic crania[3] we found calvarial sclerosis, as evidence of lasting hypopituitarism, ten times more frequent in females than in males. In a group of 45 cases similarly studied in the University Clinic, Royal Victoria Hospital, Montreal, where again the cranial and physiological diagnoses showed a high correspondence, we found calvarial sclerosis in dyspituitarism to be six times more frequent in the female. Thus, this group (selected because they manifested a nasal disease of unknown etiology, the locus of which is cranial), in which the evidence of pituitary disturbance is derived from the cranial skiagram alone, characteristically resembles in this respect two other groups examined in which the cranial evidence of dyspituitarism was in a large percentage of cases confirmed by physiological findings.

Returning to the question of the etiology of the nasal disease, the fact stands out that the cranial skiagrams offer evidence in half of the males, and in more than three-quarters of the females, of a hypopituitarism which has left its imprint upon the cranium, with evidence that this state obtained in the first two decades of life, in certain cases being recognizable in the middle of the 4th decade.

Despite the smallness of this series, we feel that the above facts represent not only the true state of affairs in this group, but in all likelihood are also true for other groups studied elsewhere. The nature of the specific defects in the nasal skeleton, first accurately measured in a significant series of cases of ozæna and controlled by similar measurements in non-ozænous nasal disease and normal noses by Hopmann,[6] confirmed by Kayser[7] and Gerber;[8] the recognition of hypoplastic sphenoidal sinuses in ozæna by Hartmann[9] and the finding of generally hypoplastic sinuses in association with conchal atrophy by Bergeat;[10] the finding, in 40 cases of ozæna, of 39 with an upper facial index of 50.1 and over (chamæprosopia) and only 1 case of leptoprosopia by Meisser,[11] and his demonstration that such predominence of chamæprosopia was not found either in the same stock or in non-ozænous nasal disease; the work of Elmiger[12] and Bernfeld;[13] all these records convince us that their cases of atrophic rhinitis, had they been skiagraphed, would have fallen into types of dysplasia very similar to our own. Such facial growth failure we now know to be produced by pituitary disability in the ontogenetic growth of the patient; for the condition is not congenital, although it is familial. Zuckerkandl[14] convinced himself of this after the examination of 252 infantile skulls, on finding only one case of conchal atrophy, in a boy of 12.

In the craniometric investigations of these authors it can be seen that the disease in certain instances did occur in relatively normally developed faces. In our present series 16.6 per cent of the males and 6.8 per cent of the females show cranial skiagrams we classified as "normal", although they do show in varying degree local deformity in the middle third of the face, and some show a certain degree of sinus hypoplasia. There remains, however, a significant group in both sexes (29.2 per cent males and 9.1 per cent females) in whom the cranial skiagram cannot be called normal owing

to the fact that it shows evidence of hyperpituitarism during the period of active growth (type I dysplasia), and a residual group, already referred to (8.4 per cent males and 11.4 per cent females), who were similarly affected in growth although later they appear to have passed into a hypofunctional phase. This pituitary hyperfunction, whether transitory or not, in a frequency of undoubted significance (males 37.6 per cent, females 20.5 per cent), precludes the conclusion that atrophic rhinitis and ozæna occur necessarily, or essentially, on a background of familial hypopituitarism, even although, as we have said already, that condition in the present series appears to be a recognizable factor at one time or another in half of the male cases and in over three-quarters of the female cases.

A more likely explanation is that the disease makes its appearance as a genetically transmitted, more or less localized focal point in a special familial constitution, of the order of a dyspituitarism, produced by the mating of dyspituitary stocks—stocks in whom pituitary function is apt to be unstable in secretory activity or nature, or in time of activity. In individuals resulting from such matings the anterior pituitary tends for the most part in this disease to be underactive during the period of most marked ontogenetic development, so that cranial differentiation is apt to be defective in so far as this process affects the cranium as a whole. Particularly, it would seem that this hypopituitary state obtains during that period of growth when the respiratory needs of the growing body at adolescence are met by active growth in the respiratory part of the face. As was originally shown by Merkel[15] nasal growth at this time is chiefly on the part of the middle meatuses, which are bounded by the conchæ. Such a state of affairs would appear to have been most true and to have obtained most often in those earlier series of cases reported, and to be true for those cases in our series in which we have pointed out evidence of consistent hypopituitarism. Such hypofunction would appear definitely more to affect the female sex, the sex in which the amplitude and duration of pituitary influence in skeletal growth and differentiation is normally less marked, even although there is a brief period in the early second decade when it is ahead in time of similar influence in the male.

Normally the female cranium, in comparison with the male, is hypopituitary in type, as is the male's when compared with the crania of palæolithic man and the higher apes. It would appear also that women are more apt to suffer from hypopituitarism in spheres other than that of body growth. They are more prone to disturbances of fat and carbohydrate metabolism than men, in which conditions there is often an associated calvarial sclerosis or hyperostosis. This natural tendency would in part help to explain the relatively greater proportion of women who at one time or another give evidence of having suffered from an apparent glandular hypofunction in the present series (81.8 per cent females; 54.2 per cent males). However, if the frequency of occurrence of acromegaly in the female can be taken as an index of the frequency with which women are liable to suffer from *hyperpituitary* states, it is to be admitted that they are only somewhat behind the males in this respect, for in a total of 1,319 cases of acromegaly 49 per cent of those in whom the sex was recorded were females (Atkinson[16]). In an earlier series[3] of 274 cases of type I cranial dysplasia, which connotes a hyperpituitary state in the years of growth, 117 cases (42.7 per cent) were in females; this would seem to support the figures in actual acromegaly. Of the total group of 494 dysplastic crania in this earlier series 63 per cent occurred in females, which sex showed a very large preponderance in those dysplastic groups which afford evidence of hypofunction at one time or another. The conclusion may reasonably be drawn that women are more apt to suffer from dyspituitarism than men; that the occurrence of hyperfunction is about equally frequent in the two sexes; but that women are considerably more apt to suffer from hypofunction.

It would appear, therefore, that the present group of cases, selected on the basis of the local nasal condition, which is familial and in which there has long been recognized to be a constitutional factor, gives evidence of a constitutional background of a nature earlier demonstrated in a larger group of cases to be "dyspituitary", both groups having in common evidence in the cranial skiagram of a dysplastic condition. The word "dyspituitarism" is used to connote an instability of function which may consistently, or temporarily, tend to the side of hypofunction

or hyperfunction, or the latter followed by a phase of the former.

In dyspituitarism there is a tendency for the cranial bones to have an abnormal mode of growth, especially in certain areas. Resorption is irregular and disordered in its site, and compensatory deposition (which, depending on the nature of the defect produced, may even merit the term "healing") is apt also to be irregular in situation and excessive in amount. Such a condition may obtain not only during active growth but also in the function of bone maintenance, when dimensional growth is over; there may be excessive resorption, and excessive consolidation. We feel that it is in this way that the well-recognized pathological changes in the lateral wall of the nose in atrophic rhinitis are to be explained, that is to say as occurring on a background of constitutional dyspituitarism that may vary from one extreme of function to the other. We feel that it is the order of this variation which accounts for the occurrence of all five varieties of cranial dysplasia in this series of atrophic rhinitis.

While we may thus explain the osseous nasal changes as one of the several fruits that grow on the dyspituitary family tree, it is obvious that it does not offer as satisfactory an explanation for the mucosal changes. Speculation as to the mode by which a dyspituitary constitution might specifically influence the condition of such a morphologically specialized mucous membrane as that which covers the bony conchæ led us to revive interest in the clinically recognized naso-genital relationship, to investigate the effect of œstrogenic substances upon the nasal mucosa of the monkey, and to observe the changes that occur in the human conchæ during the sex cycle and especially in pregnancy[17, 18] (Chart 2).

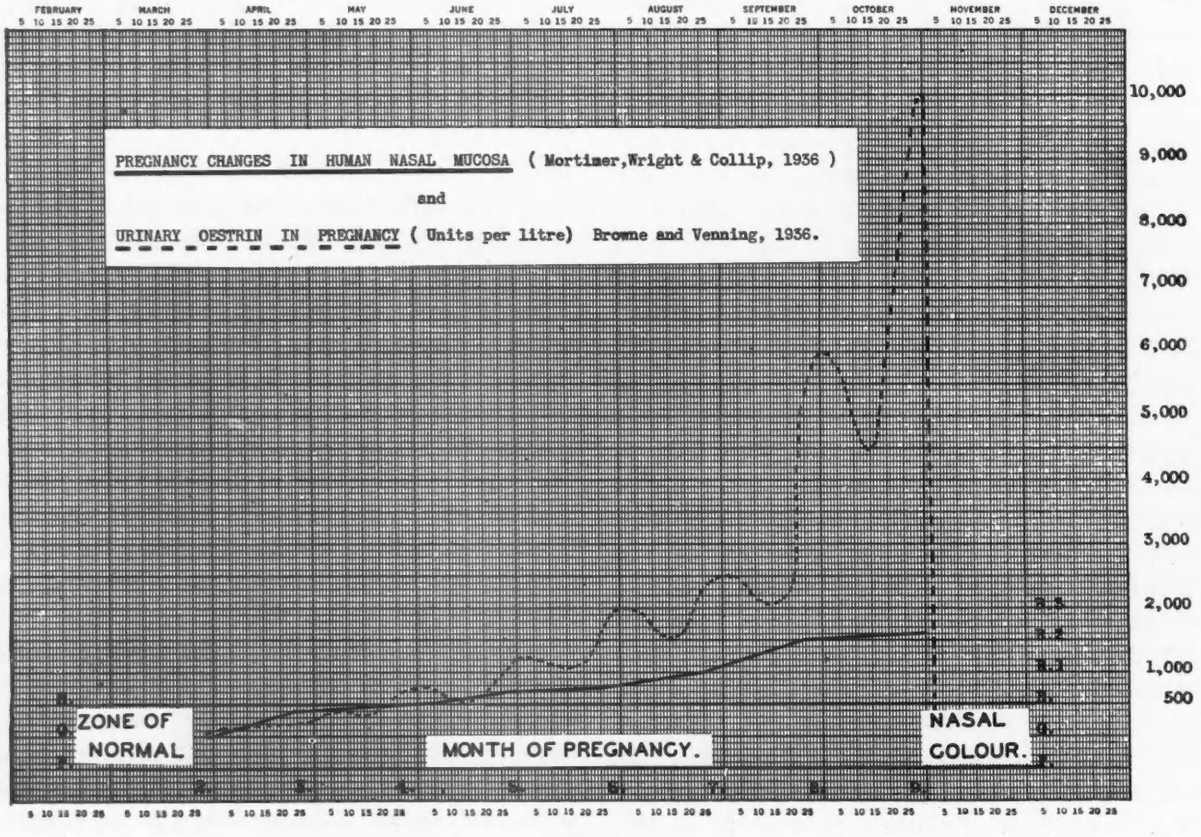

Chart 2.

The establishment of the facts that, in the monkey, crystalline female sex hormone produces changes of an order opposed to those found in atrophic rhinitis; that such changes occur normally, cyclically, in the monkey and in the nose of the human female in pregnancy, encouraged and justified the exhibition of crystalline dihydroxy-œstrin locally in cases of atrophic rhinitis and ozæna in man.

THE TREATMENT OF ATROPHIC RHINITIS AND OZÆNA WITH ŒSTROGENIC HORMONES

Keto-hydroxy-œstrin or di-hydroxy œstrin in

olive oil, 100 micrograms per c.c., is used,* precautions being taken to avoid the oil becoming rancid. Patients are given small quantities at a time, the stock supply being kept in the ice box. When the nose has been cleaned the oil is applied with a nasal atomizer, the reservoir of which is of the test-tube type, preferably graduated in c.c., so that dosage may be controlled, the patient being instructed to use about 0.25 c.c. in each nostril at each application.

In severe ozæna with marked crusting and excessive purulent secretion but not complicated by sinusitis, the crusts are removed with forceps twice a week at the clinic, and the patient given an alkaline spray (Seiler's) to be used twice a day, preliminary to the œstrin spray. When sinusitis is present treatment is first directed towards its relief either by surgical or other measures; when the maximal effect has been secured and the local nasal condition persists œstrin treatment is given.

Usually in a period of two to six weeks considerable improvement can be noted; crusting disappears, as does the odour. The discharge becomes less purulent and more normally mucoid in character, and, apparently, less in amount. But it has to be kept in mind that, with the disappearance of the crusts, the secretion may be lost, either post-nasally or by expulsion anteriorly, prior to examination. In time the mucosa presents a more normal appearance; it loses its pale greyish, œdematous character, and comes to have a pink, glistening colour. Such improvement in a chronic case is very striking, and clinically is described as "x x x". As this occurs, treatment is reduced to once a day and the Seiler spray is withdrawn; depending on further progress the œstrin spray is continued, withdrawn, or reduced in frequency of application. In non-fœtid atrophic rhinitis, the œstrin spray is used once or twice a day, depending on the severity of the local condition; the Seiler spray is not given. As improvement occurs treatment is reduced or suspended. Many patients with this condition complain of the subjective symptoms of pharyngitis sicca, nasopharyngeal irritation and inability to remove the tenacious secretion. The œstrin spray is discontinued when these symptoms are relieved.

The results of œstrogenic hormone insufflation.—In Table IV is given a roll of all female and male patients suffering from atrophic rhinitis and ozæna seen in the Oto-Laryngological Clinic of the Montreal General Hospital during the past two and a half years, with a brief description of the local condition, its duration, earlier treatment, the result of such treatment, a statement as to whether œstrin treatment has been given or not, and the duration and result of such treatment. From examination of this roll certain facts become apparent.

As regards the frequency of occurrence of the disease in an average general hospital population, in a period of two and a half years, 69 cases do not indicate that the condition is very common. It would appear that the condition is almost twice as frequent in the female as in the male, and although this appears to support the earlier observations some doubt of this does arise from the fact that while 69 per cent (31 cases) of the females seen could be given œstrogenic treatment, because of their attendance, only 29 per cent (7 cases) of the males could be so treated, and in these attendance and carrying out of treatment was clearly less regular; as a consequence the results were poorer. There are undoubtedly two factors in this; on account of their occupation males are less free to attend a clinic during working hours, and working-class males may be less fastidious in their personal condition. Without exception, the series is composed of persons who are otherwise in good health, and whose diet, vitamin intake and hygiene are satisfactory.

Paranasal sinusitis, which has been held as of etiological importance, was carefully looked for, its diagnosis depending upon clinical symptoms, radiological examination, and, in the case of the antrum, on the result of antral lavage. It was present in 17.7 per cent of the females (8 cases, 2 of which were doubtful), and in 45.8 per cent of the males (11 cases); or in 27.5 per cent of the total series.

* The œstrin preparations used were:

1. A non-crystalline material prepared in this laboratory from pregnancy urine, consisting in the main of a mixture of œstrone (keto-hydroxy œstrin) and œstriol (trihydroxy œstrin).

2. Crystalline œstrone from Prof. Girard, of Paris.

3. Dihydroxy œstrin (œstradial) kindly supplied by Dr. Schwenk of the Schering Corporation, Bloomfield, N.J.

TABLE IV.

FEMALES

Case No.	Age	Cranial type	A.R.	Ozæna	Sinusitis	Duration	Earlier treatment	Result	Œstrin treatment	Duration	Result
1	16	III	X	X	0	4 years	Radium (2)	Odour gone, crusts remain.	No	....	Not seen since May, 1935.
2	31	IV	X	X	0	5 "	" (5)	Odour gone, crusts persist.	No	....	Last seen Oct., 1935.
3	22	IV	X	X	X	15 "	" (4) antral. lavage	Unsatisfactory	Yes	1 week	Too early.
4	13	III	X	X	0	Childhood	Radium (1) costal transpl.	Poor	No	....	Last seen Aug., 1935.
5	13	III	X	X	0	5 years	Radium (2)	Odour and crusts remain.	Yes	18 months	Extremely slight crust, healthy mucosa, XXX.
6	45	IV	X	sl.	Oto-sclerosis	"years"	" (2)	Odour gone, crust remain.	Yes	18 "	XXX (tinnitus improved).
7	25	IV	X	XX	Oto-sclerosis	15 years	" (4)	Ozæna gone, crusts remain.	Yes	8 "	XXX.
8	21	IV	X	X	0	"years"	No	....	No	....	Last seen June, 1935.
9	43	IV	X	X	0	"	Radium (2)	Improved	No	....	Case of mild Graves' disease.
10	49	I	X	0	0	"	Routine	Unsatisfactory	No	....	Last seen Aug., 1935.
11	30	V	X	0	0	"	No, also def. oto.	....	No	....	" " " "
12	15	I	X	X	0	Few years	Radium (1)	Much improved	No	....	Last seen Sept., 1935.
13	12	III	X	X	0	From infancy.	" (4)	Some improvement, marked crusts.	Yes	18 months	XXX.
14	15	III	X	X	0	From infancy.	No	....	Yes	15 "	XXXX (practically cured).
15	55	II	X	0	0	45 years	"	....	No	....	....
16	20	IV	X	X	0	Childhood	Local	....	Yes	15 months	XXX.
17	28	V	X	sl.	0	"years"	No	....	Yes	15 "	XXX.
18	26	V	X	0	0	"	"	....	Yes	15 "	XXX.
19	30	V	X	0	0	"	"	....	Yes	15 "	XXX.
20	22	IV	X	0	0	"	"	....	Yes	15 "	XXX.
21	29	IV	X	0	0	18 years	Radium (3)	Improved	Yes	17 "	XX.
22	35	IV	X	X	X	Childhood	" (1)	Bad	Irregular	18 "	Odour and crusts persist
23	13	Ia	X	X	0	Childhood, mother atrophic.	No	....	Yes	17 "	XXX (frequent epistaxis during treatment).
24	20	II	X	0	?	"years"	No	....	Yes	Once	....
25	35	IV	X	X	0	"	"	....	Yes	14 months	XX.
26	6	N	X	X	0	2 years	"	....	Yes	6 "	XX—XXX.
27	29	N	X	0	0	"years"	"	....	No	....	
28	14	III	X	0	0	7 years	"	....	No	....	
29	14	IV	X	X	0	Childhood	"	....	Yes	13 months	XXX.
30	28	IV	X	X perforated septum	0	"years"	"	....	Yes	10 "	Poor (treatment neglected for 5 months).
31	34	V	X	0	0	"	Routine	Some improvement.	Yes	5 "	Nose clean, improved XXX.
32	66	IV	X	X	0	"	....	....	Yes	6 "	XXX.
33	8	I	X	0	0	1 year	No. Physical and mental precocity, mother and brother also atrophic rhinitis.	....	Yes	6 "	XXX.
34	21	IV	X	X	0	"years"	Radium (1)	Improved, crusts remain.	Yes	4½ "	XXX.
35	47	II	X	X	0	"	Various	Poor	Yes	3 "	XXX.
36	19	II	X	0	X	3 years	Antral lavage and washings.	Doubtful	Yes	2½ "	Improved XX.
37	36	IV	X	X	X	absent 1 yr.	Radical and endonasal antral oper.	....	Yes	3½ "	XX.
38	27	IV	X	0	0	"years"	Routine	....	Yes	1 "	Discharge less, improved X.
39	32	IV	X	0	0	6 months	N.S. and Ung.	....	Yes	7 weeks	XXX.
40	39	V	X	X	0	23 years	Various	Poor	Yes	2 months	XXX.
41	36		X	0	X	20 yrs. plus	Various (sinus drainage).	Improved	Yes	18 months	XXX (also oto-sclerosis).
42	7	III	X	X	X	1 year	Antrum	Poor	No	....	Last seen Jan., 1937.
43	13	N	X	X	0	1 "	Various	"	No	....	" " Dec., 1935.
44	39	IV	X	0	0	"years"	Unknown	....	No	....	" " " "
45	41	II	X	X	?	"	....	....	Yes	1 week	Too early.

TABLE IV.—*Continued.*

MALES

Case No.	*Age*	*Cranial type*	*A.R.*	*Ozæna*	*Sinusitis*	*Duration*	*Earlier treatment*	*Result*	*Œstrin treatment*	*Duration*	*Result*
1	50	I	X	X	X	Childhood	Various, endo-nasal operation.	Poor	No	....	....
2	59	IV	X	0	0	"years"	Various	"	Yes	Just begun	Too early.
3	14	III	X	X	X	3 years	Routine washes	"	No	....	Last seen Oct., 1935.
4	32	III	X	X	X	"years"	Radium (1) oper. Radium (2) ivory sloughed. Trans-plantation (sep-tum). Other nostril good.		Yes	2 months	XX.
5	15	III	X	0	X	2 years	No	....	No	....	Last seen 1936.
6	17	I	X	X	0	Childhood	Radium (2)	Improved	No	....	" " Nov., 1935.
7	10	N	X	0	0 Oto-sclerosis	"	Routine	....	No	....	" " " "
8	13	I	X	0	0	1 year	No	....	No	....	" " Oct., 1935.
9	10	I	X	0	X	3-4 years	Various	Indefinite	No	....	" " July, 1936.
10	25	I	X	0	0	Childhood	No	....	No	....	....
11	33	I	X	0	0	"years"	"	....	No	....	....
12	18	IV	X	X	0	Childhood	Routine	Slight improve-ment.	No	....	Last seen Oct., 1936.
13	16	I	X	X	X	"	Radium (1)	Improved	Yes	3 months	XXX. First seen Feb., 1936.
14	23	N	X	0	0	"years"	Routine	Poor	No	....	Last seen April, 1936.
15	20	IV	X	X	X	"years"	Lavage	Improved	No	....	" " May, 1936.
16	21	N	X	X	X	12 years	Various	Very poor	Yes	10 months	X (correspondence).
17	13	III	X	0	0	Childhood	Routine	Poor	Yes	3 "	XX.
18	12	N	X	X	0	3 years	Various	"	No	....	Last seen Dec., 1935.
19	9	III	X	X	X	2 "	"	"	No	....	" " Jan., 1936.
20	40	II	X	0	X	"years"	Unknown	....	No	....	Seen once since 1935.
21	10	III	X	X	X	2 years	Various	Poor	No	....	Last seen Jan., 1936.
22	11	III	X	0	0	5 "	"	"	No	....	....
23	23	II	X	X	0	"years"	Many	Ineffective	Yes	12 months	XXX plus.
24	12	III	X	0	0	3 years	Sprays	Unknown	Yes	2 "	Unknown.

For convenience in tabulation, the results of treatment have been expressed by the cipher X as follows: X indicates disappearance of odour but persistence of crusting and purulent secretion, although definite clinical improvement is present. XX indicates disappearance of odour, well marked decrease in purulent secretion but slight crusting remaining. XXX indicates disappearance of odour, absence of crusts, absence of purulent secretion; secretion is slight, dry and mucoid. The mucosa is pink, glistening and almost normal in colour. XXXX indicates no odour, no crusts, no purulent or excessive mucoid secretion; mucosa appears entirely healthy. Wide nasal passages constitute the only abnormality.

TABLE V.

TREATED CASES OF OZÆNA AND ATROPHIC RHINITIS

Females (of 45 cases)		*Males (of 24 cases)*	
Result	*Cases*	*Result*	*Cases*
X	1	X	1
XX	5	XX	2
XXX	19	XXX	1
XXXX	1*	XXXX	1†
Treatment too short for judgment	3		2
Poor	2		
Total	31		7

*Case 14, a girl of 15, was one of the worst cases of ozæna in the clinic records. Crusting was so marked in both nostrils as almost to justify an anæsthetic for their removal; it took two months for complete removal of the crusts with forceps. The condition had been present "since infancy" and there was no record of what earlier treatment had been. She has been attending the clinic for 15 months. Today the only evidence of abnormality in the nose is the abnormal width of the passages; the condition so far would seem to justify the clinical description of "practically cured".

†Case 23, a male aged 23 years, a medical student. Purulent discharge was profuse and crusting so marked that he described them as "casts the size of the end of the thumb". He had had the condition since about puberty and had had many forms of treatment without any very marked improvement. He has been treated for about a year; he is intelligent and co-operative. After initial improvement he was treated with plain olive oil, without œstrin, and the condition regressed. At the moment of writing, apart from abnormal nasal width, the nasal condition is "cured", and he has not used either œstrin or other nasal treatment for five weeks.

In arriving at an estimate of the efficacy of this treatment it is evident that the male series is too small to do more than demonstrate the fact that the male conchal mucosa does respond to female sex hormone, applied locally, just as the mucosa in the male monkey reacted to œstrin, injected hypodermically.[19] However, the effects of œstrin treatment in atrophic rhinitis is clearly evident in the female series. Of 31

cases so far treated, 19 per cent (6 cases) have shown definite improvement, while 64.5 per cent (20 cases) have shown disappearance of odour, absence of crusts, disappearance of purulent secretion, the remaining secretion being slight, dry and mucoid; the mucosa is pink, glistening and almost normal in colour. It should be noted that of this number 20 were suffering from ozæna.

Dr. G. E. Hodge and the rhinologists of the Department, who have had an opportunity of following the cases treated, are of the opinion that œstrogenic hormone insufflation is a considerably more effective treatment for ozæna and atrophic rhinitis than any other available until now. On the basis of the experimental work on the monkey, already referred to, it is reasonable to suppose that this treatment induces a hyperæmia, an increased glandular activity in the mucosa, and, perhaps, in time, an actual increase or hyperplasia of the mucosal glands. While the clinical appearances would seem to justify such a thought, it is to be clearly understood that so far we can offer no histological evidence of this from biopsy material.

If one were to offer a speculative explanation, one might suggest two possibilities to account for the clinical results. First, the hypofunctional phase of the constitutional dyspituitarism, present at one time or another in so many of the cases, may result in a depressed ovarian function, or a delay in the gonadotropic influence of the pituitary on the gonad at puberty. Certain of our cases with primary amenorrhœa would seem to suggest this, but beyond this, we have no evidence for such a view. The question can only be settled by hormone assays on a significant number of cases, an aspect of this investigation which we hope to carry out in time. Secondly, there may be in such as develop the disease a relative loss on the part of the conchal mucosal cells of the phylogenetically acquired capacity of specific response to normal quantities of œstrin in the blood. In the course of phylogenetic development man has almost completely lost the capacity of "skin" response to circulating sex hormone, which is so strikingly retained in the perinæum, nipple, face and nose in certain modern primates. Nasal response, however, can still be seen in normal cyclic women, and especially in pregnancy. Compared with the monkey, this functional capacity has apparently largely become recessive, and it is possible that those who are prone to develop atrophic rhinitis have a more marked recession, to the point where response to normal œstrin concentrations in the blood, essential to the full differentiation of the conchal mucosa in ontogenetic growth, is lacking. That this capacity, however, is not entirely lost is shown by the reaction which takes place when the hormone is allowed to exert its specific influence locally in concentrations which, while slight in terms of absolute dosage, are relatively high at the site of absorption. With so many facts necessary to the full knowledge of the etiology of this disease still lacking, we are inclined to the view that the beneficial effects of the œstrogenic therapy in atrophic rhinitis, which we bring forward here, are due, despite the pathological condition of the mucosa, to the persistence, although perhaps in diminished form, of the inherent capacity of the conchal mucosa to respond to a stimulus which has become specific in the phylogeny of the species.

There may, however, be certain disadvantages in this therapy and even, conceivably, certain dangers. As in all new treatments, blind empirical use in all cases should be discouraged. Like all endocrine treatment it is more suited to the hand of those who have the knowledge and the means of estimating by test the patient's physiological status before and during treatment, so that more may be learned of its action and applicability.

During the first week of treatment complaint may be made of headache; this has occurred in about a third of the cases. It may be "frontal" or "temporal", fleeting or lancinating. It seems mostly to occur in patients showing type III or type IV cranial dysplasia. As a rule in such cases the body of the sphenoid is poorly differentiated, the sphenoidal sinus is apt to be hypoplastic, and the sella turcica is small, with apparent clinoid "bridging". In view of the free lymphatic communication between the nasal fossæ and the cranial cavity the possibility arises that such headache may be indicative of pituitary hyperæmia and swelling. Experimentally, it has been shown that œstrogenic hormones may produce vascular and other changes in the anterior pituitary, and elsewhere[20, 21, 22] when given in large doses to animals. It is not suggested, with the small doses

given nasally, that it would be reasonable to fear either causing damage to the pituitary or exciting a carcinogenic effect. The dosage given is very much smaller and treatment continues for no longer than today is routine practice in the treatment of certain endocrine gynæcological conditions. The headache can usually be controlled by decreasing the frequency of treatment. As a rule it is not a persistent feature, although cases have occurred where the patient abandoned treatment on account of it.

Certain patients have shown frequent slight epistaxis during treatment, and without doubt due to it, recalling the spontaneous epistaxis of pregnancy. This causes no great inconvenience or danger, and may be taken to indicate an active mucosal response to the treatment.

Finally, a fact of great interest became apparent in the course of this investigation; seven patients were found to suffer from progressive deafness in addition to atrophic rhinitis (female cases 6, 7, 11, 14, 16 and 18; and male case 7—Table IV). Female patient No. 6 reported improvement in tinnitus during treatment for the nasal condition. Seventy cases of progressive deafness have been studied; in the cranial skiagrams there is evidence that in both diseases there is the same constitutional background. An oto-genital relationship is suspected since treatment in certain cases has given encouraging results, particularly in respect to tinnitus. One case of oto-sclerosis and marked hypertrophic rhinitis occurred.

SUMMARY

1. Study of the cranial skiagrams of 68 cases of atrophic rhinitis and ozæna gave evidence in a large majority of a dyspituitary state during or subsequent to the growth period.

2. It is suggested that the disease occurs as a genetically transmitted, more or less localized, focus in a special familial constitution, produced by the mating of dyspituitary individuals, in whom anterior-lobe function is unstable in secretory activity, nature or time of activity. It is on this basis that the nasal osseous changes are to be understood.

3. Speculation as to the mode by which a dyspituitary constitution might influence the morphologically specialized conchal mucosa led to the investigation of the naso-genital relationship in the monkey, and recognition of the fact that administration of œstrogenic substances produces a specific response in the conchal mucosa, closely akin to that resulting in other "sex-skin" areas, as already reported.

4. That such specific changes are of an order opposed to the pathological changes occurring in atrophic rhinitis justified the exhibition of dihydroxy-œstrin locally to the nose in this disease.

5. Thirty-one female and 7 male patients were available and treated, with results justifying the conclusion that in œstrogenic hormone insufflation there is to be found a therapy for ozæna and atrophic rhinitis considerably more effective than any other till now available.

6. Seven patients were found suffering from both atrophic rhinitis and progressive deafness; an eighth case showed both oto-sclerosis and hypertrophic rhinitis.

The authors wish to express their appreciation of the very helpful cooperation given them in this work by Dr. G. E. Hodge, Dr. F. W. Shaver and Dr. G. E. Hilton, of the Department of Oto-Laryngology, in the clinical examination of the cases; and by Dr. W. L. Ritchie, Dr. J. W. McKay and Dr. E. M. Crawford, of the Department of Radiology, Montreal General Hospital, in the radiological study of the patients.

GENERAL DISCUSSION

1. The question was asked whether œstrin in oil would be a suitable treatment for certain cases of premenstrual colds of the type of vasomotor rhinitis.

It was pointed out that, on the basis of the experimental work on the monkey, this treatment would be contra-indicated in such cases. Administration of œstrin hypodermically in the monkey produced in the conchæ engorgement and swelling; in addition there was evidence that a more moderate engorgement and swelling normally took place in the monkey physiologically, and that this was premenstrual in time. There was also evidence that such reddening and swelling occurred normally, premenstrually, in the human female, and that such a condition was associated with the rise of the œstrin tide in the blood. Such abnormal physiological conditions, as indicated in the question, conceivably might be due either to an abnormal œstrin production at this time or to an idiopathic hypersensitivity of the nasal mucosa to normal œstrin production. Both these suggested mechanisms would contra-indicate the exhibition of œstrin either locally in the nose in oil or hypodermically.

2. Dr. Pentecost, Toronto, asked whether the good results of treatment with œstrin in oil in cases of atrophic rhinitis were due to irritation of the nasal mucosa, or to absorption and a general effect of the hormone making good a possible deficiency of gonadotropic influence of the pituitary gland.

In reply it was stated that the experimental work on the monkey already referred to had demonstrated that œstrin produced a specific response in the conchal mucosa and sub-mucosa; that the dose employed, namely, 100 gamma per c.c., while adequate for eliciting a local nasal response, would be too small as replacement therapy in hypothetical cases of hypogonadism secondary to primary anterior lobe pituitary gonadotropic deficiency.

3. A third question was asked as to the efficacy of the œstrin treatment when the atrophic rhinitis was complicated by marked sinus infection. Dr. Wishart, Toronto, asked how the well recognized improvement which follows the use of hypertonic saline was to be explained. Also he pointed out that in many of the cases he saw in school children there was co-existent

ethmoid sinusitis, and he doubted very much if the spray could be made to reach the mucosa of the ethmoid labyrinth. He also asked an explanation of the condition of saddle-nose in children who have no atrophic rhinitis.

In reply, it was pointed out that not only hypertonic saline but a number of other agents capable of producing either glandular activity or vascular changes of an order opposed to the ischæmic condition of the mucosa in atrophic rhinitis undoubtedly did produce improvement. Among such substances acetylcholine did so act in virtue of the marked vasodilatation it produced. It was, however emphasized that with œstrin the vasodilatation and glandular stimulation in the mucosa was produced specifically; that it was probably not due to vasomotor influence through the sphenopalatine ganglion as the work of Bachman *et al.* has shown.[19] These authors demonstrated that the response in sex-skin areas was inherent in the cells of such specialized sex-skin areas, amongst which the nasal conchæ must be included, and that this specific capacity of response to œstrin had been acquired in phylogeny. By means of a two-staged pedicle graft operation Bachman transferred pubic sex-skin to the anterior abdominal wall about the region of the umbilicus. When healed in its new site this piece of skin had a new blood supply and its old innervation in the pubic area was cut, yet on the administration of œstrin hypodermically it responded in the classical way. He also demonstrated the converse to be true, that a piece of non-sex-skin grafted by the same surgical procedure into the pubic sex-skin area did not share the sex-skin response to œstrin. Also, it had recently been demonstrated by Zuckermann in London that a higher concentration of free œstrin could be demonstrated in the cyclic monkey in sex-skin than in non-sex-skin.

With reference to the question of the treatment benefiting cases complicated by ethmoid sinusitis it was pointed out that not only was it unlikely that the spray would reach such areas, but that, even though it did, it could not be expected to produce beneficial results in as much as that to the speaker's knowledge the specific response to œstrin would appear to be limited to the conchal mucosa.

In regard to the occurrence of saddle-nose, the typical deformity in well marked cases of ozæna and atrophic rhinitis in childhood, in the absence of any evidence of atrophic rhinitis, it was pointed out that not only syphilis but many other conditions capable of affecting the differentiation of the face in childhood could produce such deformity; the enumeration of these would not add materially to the discussion. However, it was Dr. Mortimer's view that in order to produce atrophic rhinitis plus the saddle-nose deformity there had to be present at least two factors, one of which produced the nasal deformity. It had been demonstrated that in many of the cases the background constitution was dyspituitarism, although it was also felt that the marked expression of this constitution in the middle third of the face was probably genetically transmitted.

With regard to the mucosal defect it would appear that another factor was at work in which the sex-gland function was implicated. A dyspituitarism could conceivably in certain cases produce a hypogonadism which might directly affect the nasal mucosa, but that so far the speakers had no proof of this. This question would have to be investigated by hormone assay in cases suffering from the nasal condition. It was also possible that there might be locally, in the mucosal cells, a spontaneously occurring lack of response or insensitivity to œstrin. This, however, was pure speculation.

In replying to Dr. Wishart's question as to the efficacy of this treatment in cases complicated by profuse sinusitis not necessarily of the ethmoid cells, Dr. Wright said: "In these cases, with normal or larger than normal sinuses, associated with infection, the bacterial flora has the power of breaking down protein material and causing an offensive odour. These cases have to be treated in the same way as any suppurating sinusitis, namely, by radical surgery and close follow-up. They are extremely difficult to cure and usually the odour persists."

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TOTAL THYROIDECTOMY IN CARDIOVASCULAR DISEASE.—R. Singer reports a number of cases of cardiovascular disease in which, after all medical treatment had failed, considerable improvement was obtained following total thyroidectomy. The results were good in myocardial disease as well as in angina pectoris. The author elaborates the theoretical basis of the operation, which should be limited to cases of chronic decompensated hypertony which do not respond to digitalis and strophanthin therapy, and to non-progressive angina pectoris which remains uninfluenced by the usual therapeutic measures. In no case was the operation followed by cachexia strumipriva; in fact, most of the patients felt much brighter after the operation.—*Wien. klin. Wschr.*, July 9, 1937, p. 1025. Abs. in *Brit. M. J.*

OBSERVATIONS UPON THE EXPERIMENTAL AND CLINICAL USE OF SULPHANILAMIDE IN THE TREATMENT OF CERTAIN INFECTIONS*

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THE experimental observations of Domagk[1] showed that the hydrochloride of 4′ sulphamido 2, 4 diamino-azo-benzene (prontosil) had a marked therapeutic value in the treatment of hæmolytic streptococcal infections in mice. The Tréfouëls[2] and their associates pointed out that para-amino-benzene sulphonamide (sulphanilamide) appeared to be the effective part of the compound with which Domagk was working. The clinical observations of numerous German investigators[3, 4, 5, 6] demonstrated the value of prontosil and its soluble derivative, the disodium salt of 4′ sulphamido-phenyl-2-azo-7-acetylamino-1-hydroxy-naphthalene-3, 6-disulphonic acid (prontosil solution) in the treatment of beta-hæmolytic streptococcal infections.

Colebrook[7, 8] and his associates have studied the experimental effects of the "prontosils in streptococcal infections in mice, and their clinical value in the treatment of streptococcal puerperal fever. In both instances marked therapeutic effects were noted. Buttle[9, 10] and his collaborators have reported the effects of sulphanilamide therapy in numerous experimental infections in mice, and report therapeutic benefits in hæmolytic streptococcal, meningococcal, typhoid and paratyphoid infections. We[11 to 14] have observed striking effects from the use of sulphanilamide and its dye derivatives in the treatment of experimental and clinical hæmolytic streptococcal infection. Furthermore, we pointed out,[14] as did Rosenthal,[15] that sulphanilamide has some therapeutic effect in the treatment of pneumococcal infections in mice. Schwentker, Gelman and Long[16] reported that sulphanilamide was of definite value in the treatment of menigococcal meningitis and meningococcæmia in human beings. Recently, Dees and Colston[17] have observed marked beneficial effects from the use of sulphanilamide in the treatment of acute gonococcal urethritis in men.

Thus, at the present time there seem to be adequate experimental and clinical data for recommending the use of sulphanilamide or its dye derivatives in the treatment of beta-hæmolytic streptococcal infections, and evidence which is favourable to the use of sulphanilamide in meningococcal or gonococcal infections is rapidly accumulating.

In this report we will first discuss the use of sulphanilamide in the treatment of experimental *Cl. Welchii* (Welch bacillus) infection in mice. Then, because information regarding the use of sulphanilamide in certain infections of infancy and childhood has not been made generally available, we will outline methods of treatment suitable for children; and, finally, we will review again the toxic effects of this chemical.

EXPERIMENTAL

The strain of *Cl. Welchii* used in these experiments was obtained from Dr. Linda Lange, of the Johns Hopkins University School of Hygiene and Public Health. Transplants and serial cultures of this strain were maintained in anaerobic beef infusion broth sand cultures. The cultures were prepared as follows. About a gram of sterile sand was added to an ordinary sterile test tube. Then the inoculatum (1 c.c.) was added slowly directly to the sand in the bottom of the test tube. The wet sand was overlaid with 10 c.c. of 0.075 dextrose beef infusion broth which had been previously boiled to expel the air and then rapidly cooled. The culture was capped with sterile vaseline and incubated at 37° C. for 22 hours. A satisfactory growth of *Cl. Welchii* was always obtained when this technique was employed.

We soon found that the strain of *Cl. Welchii* which we were using was of relatively low virulence for mice when it was injected by the intraperitoneal route. One-half of a c.c. of the

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whole culture regularly killed mice within 4 to 6 hours, as did also, in one experiment, the same amount of a 2 to 5 dilution of a culture. It was evident that the introduction of the toxin facilitated the ability of these inoculata to kill in such a short period, because within 15 minutes after inoculation the mice were quite ill. Because of this we decided that it was best to pipette off the supernatant broth, centrifugalize the organisms out of suspension, and resuspend them in the same amount of broth as was contained in the original supernatant fluid. Mice inoculated by the intraperitoneal route with 0.5 c.c. of the resuspended bacilli did not as a rule sicken until an hour had passed. Death was somewhat delayed when this inoculatum was used, but generally occurred between 6 and 24 hours after inoculation.

be directly upon the microorganism and that it reduced the rate of multiplication of the clostridia *in vivo*, thus permitting the phagocytes to remove and destroy the clostridia before enough toxin could be produced to kill the mice. This effect is very rapid, and when once under way the mouse is quickly restored to health.

We have noted previously[14] that in experimental streptococcal infections the mice might die as long as 114 days after treatment with sulphanilamide had been discontinued, and that an intensive course of therapy was needed if the survival rate was to be great. This is not the case in the treatment with sulphanilamide of mice suffering from an experimental *Cl. Welchii* infection. In this instance intensive therapy over a period of 24 hours has proved ample in controlling the infection. Another

TABLE I.

THE EFFECT OF SULPHANILAMIDE THERAPY IN EXPERIMENTAL CL. WELCHII INFECTION IN MICE

Experiment Number	*Number of mice*	*Inoculation of Cl. Welchii 22-hour culture*	*Treatment commenced hours after infection*	*Total amount therapy*	*Death hours*					*Death days*		*Percentage survival*
					4	*6*	*8*	*12*	*24*	*2*	*3-14*	
1	4	0.5 c.c.	1	20 mg.	3	..	..	..	1	..	..	0
1	4	"	....	control	4	..	..	..	..	..	..	0
2	4	0.5 c.c. 2 to 3 dilution	1	36 mg.	..	..	1	..	1	..	..	50
2	4	"	....	control	4	..	..	..	..	..	..	0
3	4	0.5 c.c. suspension in broth	1	34 mg.	..	..	..	..	1	..	..	75
3	4	"	....	control	1	..	..	..	3	..	..	0
4	23	"	1	96 mg.	9	..	..	2	..	2	..	44
4	10	"	....	control	..	4	..	2	4	..	..	0
5	23	"	1	28 mg.	..	..	..	..	..	..	..	100
5	13	"	....	control	..	4	6	..	..	1	..	15
6	6	"	1	28 mg.	..	1	..	..	..	2	..	50
6	6	"	....	control	..	2	3	1	..	..	..	0

In Table I are the results of sulphanilamide therapy in experimental *Cl. Welchii* infection in mice. As can be seen, no mice inoculated with 0.5 c.c. of the whole culture survived, but when the culture was diluted slightly 2 of 4 treated mice survived. In 3 experiments in which the clostridia were resuspended in broth, 36 of 50 treated mice (72 per cent) survived, while only 2 of 27 untreated controls (7 per cent) survived the injection of 0.5 c.c. Thus, there is evidence that treatment with sulphanilamide is effective in controlling experimental *Cl. Welchii* infections in mice.

In the course of certain other studies made upon mice infected with *Cl. Welchii* we noted[18] that the action of the sulphanilamide seemed to

point of interest in this connection is that while it is well known that mice infected with hæmolytic streptococci of low mouse virulence cannot be successfully treated with sulphanilamide, yet, in the case of *Cl. Welchii*, an organism relatively avirulent for mice, such therapy is successful.

Recently, Bohlman[19] has treated 5 patients suffering from gas-gangrene infection with sulphanilamide. In each of the 5 instances the results seemed to be very good. While a conclusion as to the effect of sulphanilamide in gas gangrene cannot be determined without further clinical studies, it would seem logical, in view of the existing clinical and experimental evidence, to use the chemical in the treatment of this condition.

CLINICAL OBSERVATIONS UPON THE USE OF SULPHANILAMIDE IN THE TREATMENT OF CERTAIN INFECTIONS IN INFANCY AND CHILDHOOD

The use of sulphanilamide or its derivatives in the treatment of hæmolytic streptococcal, meningococcal or gonococcal infections in infants and children presents certain technical problems. However, as will be noted from the following illustrative case histories, it is possible to use sulphanilamide in small children without too much difficulty.

TABLE II.

CASE 1

B.B.H. Age 27 days. Weight 4 pounds, 2 ounces. Erysipelas following mastoiditis.

Date May 1937	*Time*	*Sulphanilamide therapy (grams)*		*Remarks*
		Subcutaneous (In 1/6 molar Na Lactate)	*Per Os*	
30	12 noon	0.4 in 50 c.c.	..	Temperature, 102.5° to 103 5°. Transfusion 35 c.c. citrated blood.
31	1 a.m. 12 noon 8 p.m.	0.12 in 15 c.c. 0.12 in 15 c.c. 0.12 in 30 c.c.	..	Temperature, 101° to 102°. Erysipelas receding. Slight cyanosis.
June 1	8 a.m. 8 p.m.	0.12 in 30 c.c. 0.12 in 30 c.c.	..	Temperature, 100° to 102°. Marked regression of erysipelas. Slight cyanosis.
2	12 noon	0.12 in 30 c.c.	..	Temperature, 99° to 100°. Slight cyanosis.
3	....	....	..	R.B.C. = 5.4 mil. Hgb. = 93%. Lesion gone.

In severely ill infants sulphanilamide is best given by the parenteral route, dissolved either in physiological saline, in 1/6 molar sodium lactate, or in Hartmann's solution. The chemical has a solubility of about 1 per cent at 37° C., and solutions may be prepared by bringing the solvent to a boil and then adding the required amount of sulphanilamide. The solution is then boiled for one minute, cooled to 37° C., and given by hypodermoclysis. Since the solution is unstable it should be freshly prepared for each parenteral dose. Because of the frequency with which acidosis develops during treatment with sulphanilamide in children the use of 1/6 molar sodium lactate or Hartmann's solution as a solvent is to be recommended. The hypodermoclysis should be given at intervals of 8 hours, so that proper blood sulphanilamide levels are maintained.

In other infections of infants in which sulphanilamide is used the chemical may be added to their formulas. Care should be taken that enough alkali is supplied to maintain the infants' acid-base equilibrium when the drug is given by mouth. In older children the drug may be administered in tablet form or in capsules. If difficulty is encountered in persuading the children to take the compound it may be mixed with jelly, sugar or other pleasant menstruums, and spread upon bread.

TABLE III.

CASE 2

B.B.S. Age 13 days. Weight 7 pounds, 6 ounces. Facial Erysipelas.

Date Feb. 1937	*Time*	*Sulphanilamide therapy (grams)*	*Remarks*
		Subcutaneous	
24	4 p.m.	0.3 in 40 c.c. physiological saline.	Temperature, 100.5° to 104°. R.B.C. = 4.5 mil. Hgb. = 99%. W.B.C. = 29,400. 20 c.c. 1/6 molar Na Lactate s.c.
25	1 a.m. 8 a.m. 5 p.m.	0.3 in 40 c.c. physiological saline. 0.3 in 40 c.c. physiological saline. 0.3 in 40 c.c. physiological saline.	20 c.c. 1/6 molar Na Lactate s.c. 20 c.c. 1/6 molar Na Lactate s.c. 20 c.c. 1/6 molar Na Lactate s.c. Spread of erysipelas arrested in 16 hours. Temperature, 101° to 102.6°. Cyanosis slight.
26	11 a.m. 5 p.m.	0.15 in 20 c.c. physiological saline. 0.1 in 35 c.c. physiological saline.	Temperature, 99° to 102°. Cyanosis slight. Erysipelas definitely fading.
27	11 a.m.	0.1 in 15 c.c. physiological saline.	Temperature, 99° to 100°. Erysipelas lesion practically gone.
28 to Mar. 5	....	....	Normal temperature. Discharged from hospital Mar. 5, 1937.

The amount of sulphanilamide per kilogram of body weight required to maintain an effective blood level (10 mg. per cent) in the treatment of *severe* infections of childhood seems to be greater than is the case in adults. In adults the total daily dosage required to maintain an effective blood level is 0.1 g. per kilogram of body

weight. In infants and children Shwachman[20] has found that about 0.15 g. of sulphanilamide per kilogram of body weight seems to be required for the maintenance of the 10 mg. per cent level.

CASE 1

(Sinai Hospital, No. 91425), B.B.H., Dr. Alexander Schaffer's patient, an 11-day old white boy, born 6 weeks prematurely, developed bilateral otitis media upon May 14, 1937, and a bilateral paracentesis was done. Seven days later a right mastoidectomy was performed. Upon May 29th paracentesis of the left drum was repeated. The next day there was a definite red, hot, tender, indurated advancing lesion, extending from the right mastoid wound and involving the right ear. The lesion was typical of erysipelas. The subsequent treatment and progress of the baby is outlined in Table II.

As will be noted in Table II, the child rapidly improved, and within 5 days the erysipelatous lesion was gone. It is not possible in this instance to credit the sulphanilamide with responsibility for all of the beneficial clinical effects because a transfusion had been given. It is of importance to note that, because of our fear of an acidosis developing in this small baby, we found it entirely satisfactory to dissolve the sulphanilamide in 1/6 molar sodium lactate.

CASE 2

(U.M.H., No. 56416), B.B.S., a 13-day old patient of Dr. Terry Burger, developed a rapidly spreading facial erysipelas on February 24, 1937. The lesion was red, hot, tender, indurated, with the elevated advancing border which is so characteristic of erysipelas. The subsequent course and treatment of this patient are shown in Table III.

The results of sulphanilamide therapy in this instance were very satisfactory. The erysipelatous lesion stopped advancing within 16 hours after treatment was begun and the improvement was rapid. Very little cyanosis was noted, and again 1/6 molar sodium lactate was used to

TABLE IV.

CASE 3

B.G.G. Age 6 weeks. Weight 9 pounds, 7 ounces.
Meningococcal Arthritis and Conjunctivitis.

Date May 1937	*Sulphanilamide therapy (grams)*		*Bacteriological data*	*Remarks*
	Subcutaneous	*Per Os (on formula)*		
21	.....	.....	Conjunctival smear = G – diplococci. Pus, left knee smear = G – diplococci.	Temp., 37.2° to 38° C. R.B.C. = 3.4 mil. Hgb. = 62%. W.B.C. = 14,650.
22	0.6 in 100 c.c. saline	.....	Blood culture sterile. Pus, left knee – meningococci.	Temp., 37.2° to 39.4° C.
23	.....	0.31 0.17 0.31 0.17 0.17 0.17	.....	Temp., 37.6° to 38.2° C. Blood sulphanilamide = 7.0 mg.%.
24	.....	0.17 6 i.d.	.....	Temp., 36.8° to 38.2° C. Knee unchanged. CO_2 = 48 vol. %. Definite cyanosis.
25	.....	0.17 6 i.d.	.....	Temp., 37.4° to 38.4° C. Knee less swollen.
26	.....	0.17 6 i.d.	.....	Temp., 37.4° to 38.4° C.
27	.....	0.17 6 i.d.	.....	Temp., 37.4° to 38° C.
28	.....	0.17 6 i.d.	.....	Temp., normal. CO_2 = 42 vol. %. Blood sulphanilamide = 9 mg. %. Knee markedly improved. R.B.C. = 2.5 mil. Hgb. = 50%. W.B.C. = 14,500. Nucleated R.B.C. in smear.
29	.....	.....	.....	6/1 Cyanosis absent. 6/5 R.B.C. = 3.4 mil. Hgb. = 60%. W.B.C. = 5,250. 6/6 Discharged.

control the acidosis producing effect of sulphanilamide.

CASE 3

(J.H.H., H.L.H., No. A2258), B.G.G., aged 6 weeks, entered the Harriet Lane Home on May 21, 1937. Her mother said that the "formula isn't right, bowels is bad, and she screams with left leg since yesterday." On physical examination, a conjunctivitis was found to be present, and the left knee was moderately swollen. There was not any redness or sense of local heat. The patella seemed to be floating, and the child cried out when the knee was moved. The impression upon entry was that the child was suffering from gonococcal conjunctivitis and arthritis. The subsequent course is shown in Table IV.

had had a cold. He had always been healthy and well and had had no contagious diseases.

At 4.00 p.m., March 13th, he complained of a sore throat, and by 6.30 p.m. his voice was husky, and large swollen glands had appeared upon the right side of his throat. At this time his temperature was 99° F. By 11.00 p.m. the respiratory difficulty had markedly increased and his temperature was 104.8° F. At 12.45 p.m. the breathing was markedly embarrassed. At 2.00 a.m., March 14th, the dyspnœa was so great that an emergency tracheotomy was done. At this time a diagnosis of acute hæmolytic streptococcal submucous laryngitis was made. The subsequent course is shown in Table V.

This patient's record is illustrative of the ease with which it is possible to administer doses

TABLE V.

CASE 4

D.M. Age 32 months. Weight 30 pounds. Hæmolytic Streptococcal Submucous Laryngitis, H. Influenzæ Septicæmia, Tracheotomy.

Date Mar. 1937	*Sulphanilamide and soda bicarbonate therapy grams per os*	*Bacteriological cultures*	*Remarks*
14	Initial dose 1.2 Maintenance dose 0.6 q. 4 h. Total per day 3.6.	Throat = Numerous B.H.S. Pneumococcus Type 18 Blood = H. influenzæ	Tracheotomy, 2 a.m. Resp., 36-58. Temp., 40.8° to 37.8° C. R.B.C. = 4.3 mil. Hgb. = 82%. W.B.C. = 16,400. Blood sulphanilamide level 4 p.m., 8.3 mg.
15	2.4 Sulphanilamide 1.2 Soda bicarbonate	.....	Temp., 38° to 38.6° C. Resp., 40-52. Cyanosis slight. Urine negative.
16	2.4 Sulphanilamide 1.8 Soda bicarbonate.	Blood - sterile.	Temp., 38° to 38.6° C. Resp., 40-50. Blood sulphanilamide level 9.9 mg. CO_2 = 44 vol. %. Cyanosis definite.
17	2.4 Sulphanilamide 2.4 Soda bicarbonate.	.....	Temp., 37.4° to 38.6° C. Resp., 36-48. Tracheotomy tube plugged. Cyanosis definite.
18	2.4 Sulphanilamide 2.4 Soda bicarbonate.	.....	Temp., 36.8° to 37.8° C. Resp., 28-40. Tracheotomy tube removed. Cyanosis definite.
19	Sulphanilamide 0.6 t.i.d. and 8 p.m. 1.8 Soda bicarbonate.	.....	Temp., 37° to 37.8° C. Resp., 28-36. Cyanosis definite.
21	Sulphanilamide 0.6 t.i.d. and 8 p.m. 1.2 Soda bicarbonate.	.....	.....
23	0.3 Sulphanilamide 0.3 Soda bicarbonate.	.....	Cyanosis markedly decreased.

This baby's course is interesting in several respects. In the first place, the existence of meningococcal arthritis in the absence of a preceding meningitis is uncommon. Then, this patient illustrates how easily medication can be given by adding sulphanilamide to the formula, and, finally, it demonstrates that an anæmia accompanied by evidence of bone marrow stimulation may occur in the course of sulphanilamide therapy.

CASE 4

(J.H.H., H.L.H., No. A1285). D.M., a 34 months old white boy, the patient of Dr. John Bordley, entered the Harriet Lane Home upon March 14, 1937, with a complaint of having difficulty in breathing of 8 hours' duration. During the previous two days he

of sulphanilamide in tablet form, and of the amount of the chemical required to maintain an effective blood level.

CASE 5

(Sydenham Hospital, Baltimore City Health Department, No. 22514), V.S., a 6 year old white girl, was admitted on December 4, 1936, complaining of headache and stiff neck of 24 hours' duration. She had had an earache for about a week. Physical examination showed a sick child with a stiff neck, positive Kernig and Brudzinski's signs, and a red bulging right ear drum. This was incised and free pus obtained. The lumbar puncture showed a slightly cloudy fluid containing 950 cells. No organisms could be seen in the smear, and cultures were negative. It was thought that the patient had meningococcal meningitis, and she was given 30 c.c. of antimenigococcus serum by the intrathecal route. On December 5th and 6th this treatment was repeated, but when the spinal culture of December 6th showed beta-

hæmolytic streptococci, therapy with sulphanilamide was initiated. The subsequent course is shown in Table VI.

TABLE VI.

CASE 5

V.S. Age 6 years. Weight 48 pounds. Hæmolytic Streptococcal Meningitis and Otitis Media.

Date Dec. 1936	Sulphanilamide therapy (grams) Intrathecal	Sulphanilamide therapy (grams) Subcutaneous	Cerebrospinal fluid White blood cells	Cerebrospinal fluid Culture	Remarks
6	..	....	3,100	B. H. S.	Temp. 104°. 15 c.c. antimeningococcus serum.
7	..	1.6	3,360	B. H. S.	R. mastoidectomy. Blood culture—sterile.
8	0.08	1.6	4,300	0	Transfusion of 140 c.c. blood. Marked improvement.
9	0.12	1.6	1,100	0	Transfusion of 150 c.c. blood.
10	..	1.6	450	0	Transfusion of 100 c.c. blood.
11	..	1.6	....	....	.....
12	..	1.6	1,250	0	Improvement continues.
25	..	....	....	....	Discharged.

It is probable that if this patient had been treated a month ago, rather than 6 months ago, we would have advised more frequent treatment both by the subcutaneous and intrathecal route. Our experience in the treatment of 15 cases of hæmolytic streptococcal meningitis leads us to believe that it is wise to administer sulphanilamide both subcutaneously and intrathecally at 8-hour intervals until a marked improvement is noted. It is also interesting to note in respect to this patient that we have records of 4 children ill with hæmolytic streptococcal meningitis who recovered after sulphanilamide therapy by mouth alone had been carried out.

CASE 6

(J.H.H., No. 74429), M.B., a feeble-minded white girl, aged 13 years, was admitted to the Johns Hopkins Hospital, December 5, 1936, complaining of a painful, red, swollen right leg, of 20 hours' duration. Physical examination showed a tender, red, hot, indurated lesion extending from the ankle to the knee and encircling the leg. It had a raised border. The right femoral nodes were tender and enlarged. The treatment of the patient and her subsequent course is shown in Table VII.

TABLE VII.

CASE 6

M.B. Age 13 years. Weight 70 pounds. Erysipelas Right Leg.

Date Dec. 1936	Sulphanilamide therapy (grams) Per Os	Bacteriological culture	Remarks
5	2.4	Blood culture sterile	Temp., 104.6° to 105.2°. Bromsulphalein = 0% retention. R.B.C. = 6.4 mil. Hgb. = 76%. W.B.C. = 13,500.
6	3.0	....	Temp., 101° to 103°. Erysipelas lesion improving.
7	1.8	....	Temp., 99° to 100.2°. CO_2 = 56%. Hgb. = 92%. W.B.C. = 6,000.
8	1.8	....	Temp., 98.2° to 99°. Marked recession of erysipelas lesion.
9	1.8	....	Temp., 98° to 99°. 12/10 bromsulphalein = 5% retention. 12/10 CO_2 = 49.4%. W.B.C. = 7,480. Discharged 12/19/36.

This patient represents the rapid response to sulphanilamide therapy that is seen in moderately severe streptococcal infections. It is of interest that there was little decrease in the CO_2 combining power of the blood in this patient, despite the fact that she received no alkali during treatment.

When "prontosil solution" is used for parenteral treatment instead of crystalline sulphanilamide the total daily dose should be calculated upon the basis of 1.5 c.c. per pound of body weight. The total dose should be divided into equal parts and given in 4 or 6 doses by the subcutaneous route. This amount of "prontosil solution" will colour the child's skin pink and the urine will become very red. Never administer "prontosil solution" or sulphanilamide by the intravenous route.

The importance of determining the sulphanilamide content of the blood by the method developed by Marshall[21] and his associates cannot be over estimated. In all severe infections, especially when oral therapy is being used, the blood sulphanilamide levels should be frequently determined in order to ascertain that proper levels of the drug are being maintained.

So far we have discussed the management of severe infections. In moderately severe or mild

streptococcal infections of childhood, sulphanilamide by mouth is the drug of choice. A 50-pound child, under these circumstances, will require a total of 1.6 to 2.0 g. of sulphanilamide a day; in larger children the dose should be proportionately greater. The amount of sulphanilamide may be rapidly decreased when a definite clinical improvement is noted. It is important, however, to remember that lesions of bone, such as streptococccal osteomyelitis, otitis media, and mastoiditis tend to recur if treatment is discontinued too soon, and in these diseases it is a good plan to continue with small amounts for at least two weeks after a clinical cure has been effected. It is probable that sulphanilamide will be an effective prophylactic agent in the prevention of the spread of epidemics of hæmolytic streptococcal infections. In small children one five-grain tablet, 3 times a day, constitutes a prophylactic dose of sulphanilamide, while twice this dose should be used in adolescents.

THE TOXIC EFFECTS OF SULPHANILAMIDE OR ITS DERIVATIVES

It is of utmost importance in the study of any new therapeutic agent to determine as early as possible its toxic effects. Colebrook and Kenny[7] reported that the "prontosils" had a mildly irritative effect upon the kidney, and that these compounds produced sulphæmoglobinæmia in three of their patients. They believed, however, that the association of saline cathartics with the therapeutic administration of the prontosils was a contributing factor in the production of the sulphæmoglobinæmia, and advised against the use of saline cathartics in patients receiving prontosil.

In our experience "prontosil solution" has produced but one toxic effect, namely, fever. This manifestation appears constantly in those normal subjects who have been tested with a single large dose (100 c.c.) given by the subcutaneous route. It also occasionally is seen on the third day or later of continuous prontosil solution therapy. It is our practice to discontinue prontosil solution if fever appears which is considerably out of proportion to the general clinical condition of the patient. As this generally occurs at a time when the streptococcal lesion is rapidly regressing the clinical problem involved is not difficult. We have not seen any evidence of renal irritation in patients receiving prontosil solution.

On the other hand, sulphanilamide has certain definite clinical toxic effects. In normal human beings the ingestion of 10 five-grain tablets is followed in 6 hours by slight dizziness and mild nausea. Ambulatory patients who are suffering from streptococcal infections often complain of dizziness, anorexia, nausea, and sometimes of a sensation which is described as being similar to that experienced when mildly intoxicated with ethyl alcohol. These effects, however, are rarely noted in patients who are kept in bed during the period of treatment.

A second, very frequent, toxic manifestation is cyanosis, which is sometimes associated with methæmoglobinæmia. Cyanosis has been noted in 90 per cent of the patients treated with sulphanilamide, and varies in intensity from a mild blueing of the lips to a rather intense slaty discoloration of the lips and nail beds. The mechanism of the development of the cyanosis is as yet unknown. We do not regard cyanosis as an indication that treatment should be discontinued. We have seen patients in whom cyanosis made its appearance within 5 hours after sulphanilamide had been started, and in whom it disappeared in a few days despite the fact that intensive sulphanilamide therapy was continued until convalescence was established. Previously we stated[14] that we had observed 3 patients in whom sulphæmoglobinæmia was detected in the blood. However, at the present time, there is doubt in our minds as to the accuracy of the spectroscopic determinations, and we are uncertain whether patients treated with sulphanilamide develop sulphæmoglobinæmia. The solution of this problem awaits the results of careful spectrophotometric studies which are being carried out at this time.

Practically every patient who receives sulphanilamide in therapeutic doses shows a fall in the CO_2 combining power of the blood. We have seen four cases of clinical acidosis, characterized by air hunger and an alkaline urine without ketonuria which have developed in the course of sulphanilamide therapy. This toxic manifestation of the drug has been studied in the medical clinic of the Johns Hopkins Hospital by Southworth[22] who noted that a variable but consistent drop in the CO_2 combining power of the blood plasma occurred in 15 con-

secutive cases of streptococcal infection which had been treated with sulphanilamide. This phenomenon seems to be associated with a marked loss of sodium and potassium in the urine as a result of the sulphanilamide therapy. We have found that the administration of 10 grains of bicarbonate of soda with each dose of sulphanilamide is of value in preventing the fall in the CO_2 combining power, and at the present time we regularly administer bicarbonate of soda with each dose of sulphanilamide. If an acidosis should develop the administration of 1/6 molar sodium lactate solution by the intravenous and subcutaneous routes is of definite value in combating this toxic manifestation of sulphanilamide therapy.

We have previously stated that prontosil solution may cause fever. This is also true of sulphanilamide. When this occurs it is best to stop the drug for two or three days, during which period the temperature will fall to normal if the fever is due to the sulphanilamide.

We have carefully studied the urine of patients receiving sulphanilamide without noting signs of renal irritation. As stated previously, sulphanilamide is not excreted rapidly by the damaged kidney, and hence it tends to accumulate in the blood of patients having decreased renal function. We believe that if the drug is to be used in patients with decreased renal function, the sulphanilamide blood levels should be followed at daily intervals. When the blood sulphanilamide level reaches 15 to 20 mg. per cent, the drug should be stopped.

It must be always borne in mind that sulphanilamide and its derivatives contain the benzene ring, which may damage the hæmatopoietic system in certain patients. We have seen four patients develop acute hæmolytic anæmias while under treatment with sulphanilamide in the Johns Hopkins Hospital. These anæmias were characterized by rapid development between the second and fifth days of sulphanilamide therapy, by the presence of macrocytosis, anisocytosis and poikilocytosis, by a marked increase in reticulocytes and nucleated red blood cells, and an elevated white blood count, and by jaundice in 3 of the 4 patients. Free oxyhæmoglobin was detected in the blood serum of one patient and in the urine of another. All four were treated with transfusions and all recovered promptly from their anæmias. The mechanism of the production of these anæmias is at yet unknown, but it is obvious from the finding of free oxyhæmoglobin in the serum and urine that they represent an acute peripheral hæmolysis of the red blood cells due to some unknown metabolic product of sulphanilamide. That they do not represent true idiosyncrasy is evidenced by the fact that two of the patients showed no change in their blood when given sulphanilamide again, after they had completely recovered from their infections and anæmia.

Recently, the occurrence of leukopenia and agranulocytosis in the course of sulphanilamide therapy has been reported.[23, 24] We have seen one patient suffering from a gonococcal urethritis and arthritis who developed a typical granulocytopenia, associated with an extensive angina, towards the end of the third week of sulphanilamide therapy. Upon readmission to the hospital his total white blood cell count was 1,680 cells, and the differential count showed that 16 per cent of the cells belonged to the myeloid series. No specific therapy was instituted, and within 10 days the patient's white blood cell count had returned to normal. At that time this patient was tested for an idiosyncrasy to sulphanilamide. First, 0.3 g., and a few days later 2.0 g., of sulphanilamide were administered as test doses without effect upon the white blood cells. Thus, it was impossible in this instance to demonstrate a sensitivity of the white blood cells to sulphanilamide. In this respect, the mode of action of sulphanilamide must be different from that of amidopyrine.

The occurrence of severe blood dyscrasias in patients treated with sulphanilamide has been repeatedly predicted by us. On the basis of our experience we would hesitate to advise the use of sulphanilamide unless its effect upon the blood can be carefully followed. Certainly, in the case of anæmic patients prontosil should be used with care. If the drug is recklessly or carelessly used fatalities are bound to occur.

In patients suffering from the acute toxic manifestations of sulphanilamide, we have found that large amounts of fluids act as an antidote. We have seen one patient who took 12 g. of sulphanilamide within 12 hours, and who developed headache, dizziness, nausea and a moderate degree of cyanosis. Inasmuch as we know that the chemical is excreted with water,

we had this patient force fluids, to the extent of taking 5,000 c.c. of water by mouth within a six-hour period. The drug was rapidly excreted, and after a few hours all signs of toxicity disappeared.

CONCLUSIONS

1. Sulphanilamide is an efficient chemotherapeutic agent in the treatment of beta-hæmolytic streptococcal infections, and has an indicated value in the treatment of meningococcal infections.

2. The chemical has certain dangerous toxic effects, especially insofar as the hæmatopoietic system is concerned.

3. Sulphanilamide should be used only when there is adequate bacteriological and clinical indications of the existence of an infection in which its use is supported by experimental and clinical evidence, and then with the full realization that dangerous toxic effects may result from its administration.

We wish to thank Dr. E. A. Park for his courtesy in permitting us to use the material available from the Harriet Lane Home.

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TOXIC OPTIC NEURITIS RESULTING FROM SULFANILAMIDE.—P. C. Bucy believes that a toxic optic neuritis or a toxic neuritis of any other nerve has not previously been reported as a result of the administration of sulfanilamide or of any of the related drugs in man. Likewise manifestations of involvement of the central nervous system have been limited to the observation of mental confusion. The majority of toxic manifestations that have resulted in human cases from the use of these drugs are concerned with the blood. Fever resulting from the administration of these drugs has also been recorded. Various symptoms such as urinary irritation, lassitude and dizziness, nausea, headache and abdominal discomfort have also been noted. With the exception of Borst's case, the toxic manifestations have been mild and have subsided when administration of the drug has been discontinued. However, a few of the developments have been serious and severe, if not fatal. It is obvious that sulfanilamide, though apparently a therapeutic agent of great value, has also toxic qualities of no little import which must be reckoned with. A case is cited in which a toxic optic neuritis apparently developed as a result of the administration of sulfanilamide. The fact is pointed out that some individuals seem to tolerate the drug poorly and that with the development of any of the more severe toxic manifestations the drug should be withdrawn at once. In view of the frequency with which the hæmatopoietic system is involved, it would appear advisable to make blood counts frequently, if not daily, on all patients receiving this drug. The case presented is that of a girl with osteomyelitis of the ilium who was given sulfanilamide on three separate occasions. After each administration toxic manifestations appeared: headache, cyanosis, diarrhœa and a choking sensation on the first two occasions, a severe loss of vision due to a toxic optic neuritis after administration of a single tablet (0.3 g.) of the drug on the last occasion. In each instance the symptoms subsided rapidly after withdrawal of the drug. The case emphasizes the importance of not administering sulfanilamide and any other sulphate simultaneously.—*J. Am. M. Ass.*, 1937, **109**: 1007.

ESSENTIAL CARDIOVASCULAR HYPERTENSION AS REVEALED IN EXAMINATION OF THE FUNDUS OCULI*

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IN the course of a survey of the results of special examinations requisitioned from the Department of Ophthalmology by other services in the Royal Victoria Hospital, Montreal, a wealth of valuable information has been supplied and placed on record. It was discovered, following a review of a year's work, that of the cases admitted to the Department of Medicine, 10 per cent were conditions of hypertension in one form or another, and it was considered that, in consequence, an opportunity for study offered itself with such a mass of material at our disposal. The subject has been investigated, and ably so, by many outstanding authorities, but we feel that, unintentionally, the title has been sometimes disregarded and the results in consequence beclouded because the authors failed to closely analyze or define the precise type of cardiovascular hypertension with which they were dealing. We have considered the subject under discussion, "Essential cardiovascular hypertension", as separate and distinct from such other varieties as those of nephritic and diabetic origin, as well as those from other potential sources.

Some element of appreciation of the foregoing remarks will best be grasped when it is noted that in arriving at our series of 100 cases of the essential type, 450 case reports tabulated as cardiovascular hypertension, extending very slightly over a period of more than two years' time, had to be investigated. It is to be recorded with some degree of disappointment that frequently the Department of Ophthalmology had not been requisitioned for a report on the fundus oculi. The case report in other respects invariably would be perfect in detail. Such a discrepancy, however, fortunately for your reviewers, was much more frequently the exception than the rule. Again, the cases of hypertension with an associated antecedent diabetes or nephritis far outnumbered the type of case which we had decided particularly to investigate, and these, with the errors of omission previously admitted, had to be put aside. Simply to justify our conclusions, and to attempt to draw a parallel, a series of consecutive cases of cardiovascular hypertension associated with nephritis have been analyzed, through which a comparison may be drawn and some deductions arrived at which will be referred to later.

Regarding the ophthalmological investigation, an attempt at uniformity has been made. The material supplied has been obtained without exception from that social class one finds in the public wards. Further, the ophthalmoscopic examination was carried out and the findings recorded, with very few exceptions, by the same member of the Department, and the personal error in interpretation was in consequence avoided. Again, the same type of ophthalmoscope always was used, and no findings were recorded unless the pupils were satisfactorily dilated with homatropine.

The results of our findings are registered in such detail as occasion rendered possible in the following tables.

An analysis of the hundred cases of the essential hypertensive variety compared with those of primary nephritic origin affords us the following conclusions.

In the matter of age, as one would expect, the patients with essential hypertension were definitely more advanced in years than those with the nephritic type, the average of the former being 58.7 years, and of the latter 41.4 years. The reason for this probably is that the primary nephritic cases for the most part have their origin during childhood as a result of many intercurrent diseases at that time, while the hypertensives are really the result of an ageing process. Among women the onset of the menopause is an apparent factor.

Blood pressure, at first glance, would show a seeming discrepancy, in the hypertensive

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cases at its lowest record being 160/80 and at its highest 260/120, with an average of 195.5/110.6. In the nephritic cases the lowest was 140/80 and the highest 260/170, giving an average of 219.4/131.0, the pulse pressure in the former being 84.9 and in the latter 88.4, the end-results showing a relatively slight discrepancy. As would be expected, the blood chemistry values for creatinine and non-protein nitrogen were definitely pathological in the primary nephritic cases, whereas, in the primary hypertensive cases they were essentially normal, though in a few instances high values occurred.

The specific gravity of the urine affords practically no answer to our argument. Regarding albumin, however, in primary hypertensive cases it registered from 0 to 2 plus in 50 per cent, while in the primary nephritic cases it ranged from 2 plus to 4 plus in 100 per cent. In the primary hypertensive cases, again, only 20 per cent showed casts, as compared with over 80 per cent in the latter class of case. (Table I).

TABLE I.

	PRIMARY HYPERTENSIVE CASES 100 Cases: 52 Female; 48 Male			PRIMARY NEPHRITIC CASES 17 Cases: 7 Female; 10 Male		
Data	*Low*	*High*	*Average*	*Low*	*High*	*Average*
Age	*39 yrs.*	*84 yrs.*	*58.7 yrs.*	*26 yrs.*	*58 yrs.*	*41.4 yrs.*
Blood pressure	160/80	260+/120	195.5/110.6	140/80	260+/170	219.4/131.0
Creatinine	1.01 mg.%	2.14 mg.%	1.25 mg.%	1.03 mg.%	16.8 mg.%	3.63 mg.%
Non-protein nitrogen	17.1 mg.%	75.3 mg.%	30.4 mg.%	19.1 mg.%	284.0 mg.%	90.8 mg.%
Urine specific gravity	1.004	1.036	1.017	1.006	1.030	1.013
Urine albumin	0	++	50% showed albumin	++	++++	100% showed albumin
Casts			20% showed casts			80.2% showed casts

TABLE II.

PRIMARY HYPERTENSIVE CASES—100 CASES

	Left eye						*Right eye*					
Fundus changes	*Total percentage*	*Upper nasal*	*Lower nasal*	*Upper temp.*	*Lower temp.*	*Macular*	*Total percentage*	*Upper nasal*	*Lower nasal*	*Upper temp.*	*Lower temp.*	*Macular*
Normal	29	..	..	..	..	..	28	..	..	..	..	..
Contracted arteries	63	..	..	..	..	..	57	..	..	..	..	..
Contracted arterial capillaries	1	..	..	..	..	..	2	..	..	..	..	..
Engorged veins	40	..	..	..	..	..	40	..	..	..	..	..
Tortuous veins	23	..	..	..	..	..	22	..	..	..	..	..
Buckled veins	36	..	..	8	1	..	35	1	6	2	..	..
Small petechial hæmorrhages	16	2	2	3	3	2	11	1	3	..	2	2
Large hæmorrhages	8	2	2	2	1	..	6	2	4	..	..	..
Lymph exudate	5	..	2	1	..	..	7	1	4	..	..	2
Pigment changes	1	..	..	..	..	1	1	..	..	..	..	1
Perineural œdema	5	..	..	..	..	..	5	..	..	..	..	..

Other findings:

1. Old retinal artery thrombosis—1 in O.S.
2. Venous thrombosis—1 in O.D. (upper temporal).
3. Cataracts—14 bilateral, 1 in O.S. and 1 in O.D.

To turn for a moment to an analysis of the fundus findings as recorded independently in each eye; of the 100 cases, 28 were normal on the right side, while 29 were normal on the left. These figures convey the impression that the two eyes were normal in the same number of cases. Those showing pathological findings are interesting through the various subsections. Table II shows that each eye practically balances with its fellow regarding the numbers of pathological manifestations. Also there is practically little discrepancy except in the recorded number of small petechial hæmorrhages, the left eye showing relatively more than those noted in the right. An explanation is offered which may account for such a result, in that the left common carotid artery comes off the aorta directly while the right is the branch of the innominate artery. Thus, one would expect a greater arterial hydrostatic thrust in the left common carotid artery. Regarding the question of buckled veins, Fishberg and Oppenheimer[1] would have us believe that buckling as such does not exist, and that a pressure of the relatively more contracted artery exerts little if any influence upon the underlying venous wall. They claim that the impression conveyed through the ophthalmoscope is due to a displacement of the vein to a deeper or lower level within the retinal tissue. If one is to accept that these two types of vessels occur normally within a similar stratum it is rather difficult to understand how the veins can suffer such an alteration in tissue displacement. Again, as we so frequently noted in our observation, some of the most manifest instances of buckling take place in the vein less than a disc diameter distance from the disc margin. And if both the artery and the vein are, so to speak, anchored at one end, it would seem most improbable that a decompression at such a relatively short distance from the disc could be brought about. The statements of Foster Moore,[2] as well as the pathological work of Coates[3] and Oatman,[4] with the various microphotographs illustrating actual buckling, would support the stand we take in such an argument.

Where many manifestations of a pathological process have been observed of a similar condition, such as the occurrence of buckled veins and small petechial hæmorrhages, naturally the recorded findings do not tally with the total percentage, as it was in many instances quite impossible to make absolute record of each specific lesion. For the most part hæmorrhages and exudates were found in the posterior part of the retina, relatively close to the nerve head, thus confirming the findings of Foster Moore.[2]

TABLE III.

Diagnosis	*Percentage*
Arteriosclerosis with hypertension	84
Myocarditis	29
Essential hypertension	16
Auricular fibrillation	5
Coronary thrombosis	6
Nephritis (secondary to hypertension)	2
Cerebral hæmorrhage	7
Cerebral thrombosis	14
Subarachnoid hæmorrhage	1
Pre-senile dementia	1
Syphilis	6

The medical diagnoses associated with the condition of essential hypertension speak for themselves (see Table III). Because of the verbal statement of Dr. J. C. Meakins, Director of the Medical Clinic of McGill University, that in his experience cerebral accidents were for the most part associated with a normal fundus, we were led to examine these cases rather closely. Of our 100 cases, 21 might be classed as cerebral accidents, that is, cerebral hæmorrhages or cerebral thrombosis. From Table IV

TABLE IV.

CEREBRAL ACCIDENTS—21 CASES

Fundus changes	*Left eye*		*Right eye*	
	Total	*Percentage*	*Total*	*Percentage*
Normal	6	28.6	6	28.6
Contracted arteries	13	61.9	13	61.9
Contracted arterial capillaries	1	4.8	1	4.8
Engorged veins	12	57.1	12	57.1
Tortuous veins	7	33.3	7	33.3
Buckled veins	9	43.6	10	47.6
Small petechial hæmorrhages	3	14.3	1	4.8
Large hæmorrhages	0	0	1	4.8
Lymph exudate	1	4.8	1	4.8
Pigment changes	0	0	1	4.8
Perineural œdema	2	9.6	2	9.6

it will be found that 28.6 per cent of these cases had normal fundi, which compares almost exactly with the number in the whole group of hypertensives. These two groups tally almost exactly, except in two characteristics which are easily explained. A relatively great increase

was found among the cases of cerebral accident in the number of engorged, tortuous and buckled veins, probably as a result of a general backing up of venous blood caused by the increased intracranial pressure. In the whole group of primary hypertensives there were 5 cases of perineural œdema; 2 of these were found in cerebral accidents, and are again probably the result of the increased intracranial pressure. Larsson,[5] it may be remarked, found in 11 cases of hypertension increased intracranial pressure in all. Such a condition would probably account for the perineural œdema not associated with a cerebral accident.

veins is essentially the same in the two types of case. A manifest increase of buckling in the hypertensive cases is self-explanatory, for the reason given above, as well as for the greater tissue changes occurring in the arterial wall in the first class of case. The very evident increase of hæmorrhages, both large and small, and particularly of lymph exudates, will be referred to at greater length later on. The tremendous difference in the occurrence of perineural œdema in the two conditions is simply a manifestation of a generalized œdematous process affecting all organs and all tissues as a result of nephritic disease. In the latter condition a

TABLE V.

PRIMARY NEPHRITIC CASES—17 CASES

	Left eye							*Right eye*						
Fundus changes	*Total*	*Per-centage*	*Upper nasal*	*Lower nasal*	*Upper temp.*	*Lower temp.*	*Macular*	*Total*	*Per-centage*	*Upper nasal*	*Lower nasal*	*Upper temp.*	*Lower temp.*	*Macular*
Normal.....	2	11.7	..	..	..	..	..	3	17.6	..	..	..	..	..
Contracted arteries.....	13	76.5	..	..	..	1	..	12	70.5	2	..	2	..	..
Contracted arterial capillaries	0	0	..	..	..	..	..	0	0	..	..	..	..	..
Engorged veins..	7	41.1	..	..	..	..	..	7	41.1	..	..	..	..	..
Tortuous veins...	4	23.5	..	..	..	..	..	5	29.4	..	..	..	..	..
Buckled veins...	5	29.4	..	..	..	..	..	5	29.4	..	..	..	..	..
Small petechial hæmorrhages..	10	58.8	..	..	..	1	3	9	52.9	..	1	..	..	2
Large hæmorrhages.....	6	35.4	1	2	..	1	..	4	23.5	2	2	1	..	..
Lymph exudate..	9	52.9	1	..	1	1	1	9	52.9	1	..	2	..	2
Pigment changes	0	0	..	..	..	..	..	2	11.7	..	..	..	..	1
Perineural œdema.....	8	47.1	..	..	..	..	..	8	47.1	..	..	..	..	..

It is interesting to compare the cases which we have just had under discussion with a smaller series of primary nephritic cases which have been examined regarding the same essentials as we have already noted in the former classification (Table V). The nephritic cases with normal fundi numbered 11 per cent as compared with 29 per cent in the hypertensives (left eye). It would at first glance seem to be inconsistent that a greater percentage of contracted arteries should occur in the nephritic than in the hypertensive cases. A possible explanation lies in the fact that hypertensive patients have a much thickened arterial wall due to the long and progressive existence of the disease, whereas, the nephritic is a younger person with more contractile arteries. Hence, contracted arteries would be more obvious in the former than in the latter. The frequency of engorged and tortuous

meningeal œdema results in an increase of cerebrospinal fluid, and therefore of increased intracranial pressure, which is transmitted along the optic nerve in the subarachnoid space.

DISCUSSION

Many theories have been propounded as to the pathogenesis of the various fundus changes. These have been summarized by Fishberg and Oppenheimer[1] in a recent paper, under five heads.

1. *Renal insufficiency.*—Early investigators all believed that the retinal changes came as the result of renal dysfunction. Widal, Morax and Weill[6] reported 17 cases all with nitrogen retention. However, this view is untenable as great retinal changes can take place without renal damage.

2. *Retinal arteriosclerosis.*—Von Michel[7] and other early workers believed that albuminuric retinitis is due to arteriosclerosis. This is not necessarily true, as arteriosclerosis does not always exist in such cases. This was shown anatomically by Schieck.[8]

3. *Increased intracranial pressure.*—Cushing and Bordley[9] were the first to describe a case of chronic renal disease with severe retinal lesions and a tremendously increased cerebrospinal fluid pressure in 11 cases with hypertensive retinitis. However, we believe that the retinal changes are not caused by increased intracranial pressure but are merely associated with it.

4. *Hypercholesterolæmia.* — Chauffard, de Font-Réaulx and Laroche[10] were the first to bring this theory forward. However, it is not of general validity and we merely mention it to dismiss it.

5. *Arterial hypertension.*—All the work on arterial hypertension tends to show that the tissue changes in this condition are directly explicable on the basis of hypertension alone. It was pointed out by Traube in 1861 that retinal lesions occur only in those forms of renal disease in which there is hypertrophy of the left ventricle. Fishberg and Oppenheimer[1] say that not only is it always present, but that it precedes the condition. Gowers,[11] in 1876, was the first to point out that in hypertensive states the arteries of the retina are contracted. A number of workers since then have observed spasms of the retinal arteries in hypertension, Wagenmann,[12] Elschnig,[13] Labadie-Lagrave and Laubry.[14] More recently, Haselhorst and Mylius[15] not only observed but photographed cramp-like and rapidly changing contractions of the retinal arteries in a patient with eclampsia gravidarum. After two days the contractions became more constant and involved longer stretches of the arteries. It was at this time that the first white degenerative lesions in the retina appeared.

This brings the whole problem into the realm of the rather revolutionary theories put forward by Ricker[16] some years ago. He believed that the underlying mechanism of both inflammatory conditions and hypertension was a neurovascular upset. In inflammatory conditions bacteria or other stimuli at first set up a vasoconstriction of all terminal vascular segments. But the capillaries rapidly become fatigued and relax—a fatigue paresis, exactly as one sees after an overdose of adrenalin. Then a dilatation of capillaries results, with a sustained contraction of the arterioles, which must of necessity cause a slowing of the blood stream in the capillary bed, a condition which Ricker has called, depending upon its degree, *prestasis, peristasis,* and finally *stasis,* when no blood flows. Along with their dilatation the capillaries become more permeable, an effect possibly due to anoxæmia or to opening up of stroma between the capillary endothelial cells. Krogh has confirmed these latter changes. So, depending upon the degree of slowing of the blood stream and, therefore, of the capillary dilatation, there will be progressive degrees of exudate; first, plasma and fibrin only, then white cells, and finally red cells (three stages of stasis called by Ricker, liquor-stasis, leuco-stasis, and rubro-stasis, which correspond to his prestasis, peristasis and stasis). Ricker believes that the same mechanism underlies hypertensive states. Hypertension is not caused by contraction of large arteries but of the terminal segments, the arterioles and capillaries. This has been proved by experiment. Epinephrin or sympathetic nerve stimulation produces this effect. Finally, the capillaries become fatigued and dilate. Now we have the self-same condition as is seen in inflammatory conditions. The patient becomes decompensated, to use a clinical term, œdema develops, white cells, and, if severe enough, red blood cells, appear outside the capillary wall. It is interesting to note in this regard the findings of Haselhorst and Mylius on eclamptics mentioned above. It is possible that these changes would only be seen at their best in young people whose vessels are essentially undamaged or unchanged by the normal ageing processes (such as would be seen in our nephritic group), and would not be seen in old people who have had a slowly progressive hypertension along with the normal age-period changes which would make the vessels less reactive. Of course there is that group of cases which have been called malignant hypertension. This is essentially an hypertension of explosive violence in a comparatively young person. Here one sees all the advanced retinal changes one does in a primary nephritic, the only difference being that in the latter one knows the cause of the hypertension. Of course,

in the malignant hypertensive case the neuro-vascular changes are not confined to the eye but involve the whole body and cause among other things cerebral œdema, general anasarca, and rapid destruction of such parenchymatous organs as the kidney from the perivascular tissue changes. So in these cases a nephritic factor is rapidly superimposed and maintains the hypertension, (the *primary contracted kidney* of German nomenclature, as opposed to the *secondary contracted kidney* resulting from a definite infective process).

With regard to the causation of hypertension in nephritis there has been a vigorous controversy. Some say it is due to toxæmia, and others say it is due to a reflex neuro-vascular response. A suggestive fact favouring the latter view is that in oxalate nephritis hypertension takes place if the renal nerves are intact. However, if one completely denervates the kidneys before producing the experimental nephritis hypertension does not take place. This interpretation is in accord with the old teleological hypothesis that hypertension in nephritis is due to the attempt of the body to force more blood through the kidneys.

In conclusion we should like to mention some findings in an entirely different field which might bear some relation to retinal changes. Menkin,[17] in 1934, showed that the expected cytological picture of an inflammatory exudate can be predicted from the pH of the tissues, and vice versa. For example, when the pH is on the alkaline side polymorphonuclear leucocytes predominate, whereas if the tissue becomes more acid mononuclear cells replace them and finally become predominant. We would like to offer as a possible factor in the production of retinal exudate a change in tissue pH. We have shown that in nephritis retinal exudates are more common than in uncomplicated hypertension. This is also true of diabetes. In both these conditions acidosis from time to time takes place.

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PENTOTHAL SODIUM AS A HYPNOTIC IN OBSTETRICS*

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NUMEROUS attempts have been made to help parturient woman. A din this has become, resounding, reverberating, and, lately, a clash of tumultuous conflicting opinions, at least about the barbiturates. There are too many of these, and, sad to say, innumerably many more are apt to be.[1] Malonyl-urea is susceptible to several intimate substitutions. Everybody knows what has happened since the brilliant synthesis of Emil Fischer and von Mering.[2] Tabern and Volwiler[3] have synthesized and characterized a series of disubstituted *thio*barbituric acids. They found that several of these are powerful hynotics of prompt action, from which animals rapidly recover. They stated that the sulphur in these compounds appears to accelerate their destruction in the body.

One particular malonyl-thio-urea derivative (sodium ethyl-1-methyl butyl-thiobarbiturate),

* The pentothal sodium was put up in capsules of 1, 2, 3 and 4 grains, and kindly supplied to us by Abbott Laboratories.

called pentothal, has been reported upon by Pratt, Tatum, Hathaway and Waters,[4] and by Mulinos.[5] This last investigator worked on rats, cats and rabbits. He determined the anæsthetic doses for these animals, found that this drug depresses respiration, that there is no vagus disturbance, that no irritation occurs, that muscle activity of the isolated uterus and likewise of the intestine is lessened, and the analgesia is poor. Pratt *et al.* studied the effects of pentothal on rats, rabbits, dogs, and on man. Among their findings the presently relevant ones are that pentothal causes respiratory depression, but noticeably so only in anæsthetic doses; that there are no effects on the circulatory system; that there is *no wild excitement after;* and that, as this drug is broken down so rapidly in the body, it closely approaches in its actions the so-called controllable anæsthetics. Others[6] have used pentothal as an anæsthetic, but at this time we are concerned with its behaviour in small doses, when it is essentially a hypnotic rather than an analgesic.

The work of Irving, Berman and Nelson,[7] eulogizing the benefits of nembutal as compared with several other drugs, has not fulfilled the great expectations which it excited; we ourselves have been extremely disappointed, and similar opinions about this undependable class of drugs are continually coming to our attention from most reliable sources. To be specific, even in combination with scopolamine, nembutal may cause such excitability as to necessitate the caging-in of the patient in a specially contructed bed and the employment of an attendant. This is not practical for ward cases and not conducive to good obstetrics. Again, frequently we have found that uterine contractions become definitely weakened, labour prolonged, and the use of forceps made obligatory. Further, respiratory depression in the infant is so marked that extreme resuscitative measures are often imperative.

Small wonder it is that, when some physicians give assurance of an elysian state in place of the cark and care of childbirth, woman becomes urgent in her demands for complete relief from suffering. But hazard must be considered. We feel that any sedative used in obstetrics should have no toxic effects on mother or fetus, should not inhibit uterine contractions, should not cause excitement, should produce some degree of amnesia, and should be easy of administration. Let us consider these conditions seriatim with respect to pentothal.

At once it should be noted that most of the actions of the barbiturates are referable to the brain. The liver, kidneys and blood are only slightly affected.[8] In our series of 118 cases there have been no noticeable toxic effects on mother or fetus. The maternal heart rate is invariably slowed by about 10 to 20 beats per minute, which seems to be due to the lessened excitability; the blood pressure does not change appreciably, and the urinary findings are not varied. We have observed that when the fetal heart rate is within normal limits it is not changed by pentothal, but should it be immoderately rapid it becomes somewhat slowed by this drug. All the children of this series breathed spontaneously. At this juncture it is worthy of mention that Dille[9, 10] has shown that when barbital is given to pregnant rabbits in doses less than half the minimal amount required to produce surgical anæsthesia the drug permeates the placenta just as easily as when it is given in full anæsthetic doses; that is, the placenta offers no barrier to barbiturates, and when these drugs are administered to expectant mothers the embryo will get its full share of them. This investigator measured the barbital and the amytal contents of fetus, placenta, amniotic fluid, and of maternal blood in rabbits, cats, and guinea pigs after single large doses and after repeated small doses. He found that both these drugs are transferred within the first fifteen minutes; that the permeability of the placenta goes in both directions, because when no barbiturate can be found in the mother's urine none will be found in the fetus; that the fetus behaves like an organ, barbital reaching a maximum concentration coincidently with a fall in the concentration of the drug in the maternal blood, and that the concentration of the barbiturate may reach a fairly high level in the fetus. Thus we have an explanation of the frequency of narcotized babies following the indiscriminate use of nembutal. It is true that drugs which depress the cerebral cortex do so most effectively in animals of highest development. From this point of view, in man a fetus may be thought of as a lower animal; in other words, its embarrassment relatively will not be so great as that of the mother. It is with such

thoughts that we have considered the harmful effects of pentothal on mother and child.

Concerning the influence of pentothal on uterine contractions, we have found that the drug may be started early, and that the degree of dilatation of the cervix is no guide for its administration. It is given as soon as pains are established. The duration of labour is markedly shortened, an average of 9 hours for primiparæ and of 4½ hours for multiparæ. We cannot explain it but this drug does seem to do something to the cervix, so that it dilates rapidly, and it is in the first stage of labour that time is gained. This phase has been noted independently by our nursing sisters, our residents and ourselves.

Now about excitement. We desire to emphasize this consideration most particularly, and all the more on account of what we have seen of the use of nembutal, which in chemical structure is almost identical with pentothal. With nembutal, all too often, despite careful dosage, there is marked excitement, even mania, sufficient to demand forcible restraint of the patient and constant attendance. With pentothal the woman is quiet, cooperative, easy to examine, and does not need special attention. The presence of sulphur replacing oxygen on the urea portion of the barbiturate molecule may explain the difference in the effects of these two otherwise similar substances.

Our fourth premise refers to a very vexed topic. Amnesia, analgesia, the state of the first stage of anæsthesia, or even the delirium of a second stage, while Guedel[11] knows best, how little is known of these! These matters are very difficult to evaluate. We do not strive to produce complete amnesia, nor do we believe that mothers desire it. Just as a woman does not want to forget the harmonious contentment of life forming within her, so too, concerning her travail she wants to remember, as in a cloud of light—support, comfort and deliverance—the actual fruition. She wants to perceive, but, laudably, is willing to be freed of apperception. It therefore seems permissible, together with the affectation of some psychological ritual, to administer small quantities of a minimally toxic and dependable drug sufficient to produce, at least, considerable bemusement. We feel that we have found such a drug in pentothal. With it the patient sleeps between the pains, wakes up, complains a little while they are on, and then goes to sleep again. In the case-room she is perfectly cooperative and bears down with each uterine contraction. Usually when the head of the fetus has come well down on the perineum intermittent analgesia is resorted to, for which we prefer nitrous oxide. This is often refused by the patient. She wants to have her baby. There is in most cases a certain degree of euphoria, and it is not unusual for her to sing during or after delivery. For the final part of parturition anæsthesia is produced preferably by cyclopropane. In our series of cases complete amnesia has not occurred often, but pentothal may be increased to give this effect with safety. A post-partum sedative is seldom required. In short, when pentothal is used the throes of labour are abrogated and there is serenity instead.

Lastly, with respect to the ease of administration, pentothal is given by mouth in capsule. So soon as pains are definitely established 4 grains are allowed. One-half hour later 3 grains more are given, and this amount is repeated at the end of one hour. Usually the patient now* becomes quiet, sleeps in between pains, and does the obstetrician's bidding willingly. Two or 3 grains may be repeated every half to one hour if the effects seem to be wearing off. The total quantity of pentothal used will vary from 10 to 20 grains. Latterly, at the time of the first dose of pentothal, we have given 1/100 or 1/150 of a grain of scopolamine, depending on the size of the patient, with a view to enhancing amnesia. This drug is not repeated. It may be stated here that fetal and maternal heart rates are watched closely, and the blood pressure is recorded occasionally. We are fully aware of the special benefits offered by nitrous oxide and cyclopropane for the production of analgesia during the earlier stages of labour as well as for the subsequent anæsthesia[12, 13], but these call for particular knowledge concerning their administration, and therefore may not be used so easily as the drug under consideration. It may be said here that vinyl ether is easy to give, is safe, and is suggested as a substitute for the gases in general practice.[14]

Pentothal sodium has been used 118* times in

* Since this paper was written, pentothal has been used in 120 additional obstetrical cases with equally satisfactory results.

the obstetrical department of this hospital. There were 61 primiparous women, in whom the average length of labour was 9 hours; and 57 multiparæ in whom the average length of labour was 4½ hours. Of all, the first 50 patients had no other preliminary drug than the pentothal; those following had scopolamine (grs. 1/150 or 1/100) once only at the time of the initial dose of pentothal. Two patients have had pentothal sodium by the rectum, two doses, each of 7½ grains dissolved in 25 c.c. of water, and given an hour apart. The results were as satisfactory as when the drug is taken by mouth.

SUMMARY

1. Pentothal sodium has been administered to 238 women in labour.

2. There have been no noticeable harmful effects on mother or child.

3. The duration of labour is shortened.

4. Unlike ordinary barbiturates this thio-derivative does not cause excitement.

5. Along with the hypnotic action of pentothal sodium there is usually a salutary degree of amnesia.

6. The drug, put up in capsules, is easy of administration by mouth. Also, it may be given in solution per rectum.

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NEO-NATAL MORTALITY

(A STUDY OF AN ELEVEN-YEAR PERIOD OF OBSTETRICS IN A SMALL CITY)

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FROM observations extending over twenty years in general practice the writer is convinced that the average doctor knows little about the causes of death among the new-born. In this city of just over 23,000 people there are about 40 deaths a year of babies under ten days old, including stillbirths. In Ontario 42 per cent of the babies born alive, but dying in the first year of life, disappear in the first ten days. It is unfortunately too true that the first quarter of an hour after birth is the closest to death.

A search of the records of the local registrar for the past 11 years, 1926 to 1936 inclusive, revealed the fact that there were 6,954 births with a neo-natal mortality of 453, or 6.51 per cent. When one begins to enquire why they died, the answer given in Table I is far from satisfactory.

TABLE I.

Stillbirth	155
Prematurity	146
Cerebral hæmorrhage	27
Deformities	25
Inanition	24
Toxæmia and infection	25
Difficult labour	15
Accidents to the cord	14
Atelectasis	7
Placenta prævia	7
Convulsions	6
Syphilis	2
	453

Two-thirds of them are ascribed to stillbirth or prematurity, and this proportion is raised to three-fourths if one includes those numbers opposite such terms as inanition, atelectasis and convulsions, which really throw very little light on the subject. But here in Sault Ste. Marie we

are a shade better than the province as a whole for according to the last number of the blue-book dealing with births, marriages and deaths for the year 1934 there were 1,512 infant deaths under one week and 2,091 stillbirths, and for over 90 per cent the only cause stated was prematurity, stillbirth or congenital debility. Neo-natal mortality has not diminished in the last few years, like infant mortality generally, and the first step in attaining such a desired end must be an understanding by the profession of the reason for stillbirths and neo-natal deaths, for it must be admitted from the facts mentioned above that at present we do not know.

The first point that might occur to one in thinking of this question is this. Is there much difference in the neo-mortality rate of different doctors? As an answer Table II is presented dealing with the record of 17 obstetricians who officiated at 88 per cent of the births in the 11 years already mentioned.

TABLE II.

SAULT STE. MARIE OBSTETRICIANS AND THEIR RESPECTIVE NEO-NATAL MORTALITY RATES
ELEVEN YEAR PERIOD 1926 TO 1936 INCLUSIVE

M.D.	*Cases*	*Deaths*	*Percentage*
A	51	6	11.76
B	60	7	11.66
C	347	31	9.00
D	461	41	8.90
E	420	36	8.57
F	86	7	8.14
G	501	38	7.60
H	840	60	7.14
I	218	15	7.00
J	636	44	7.00
K	794	54	6.80
L	75	5	6.66
M	462	27	5.84
N	286	15	5.24
O	223	11	4.93
P	244	12	4.91
Q	492	24	4.88
	6,121	428	7.00

Probably one might have omitted from the Table those four who had less than ten cases a year, for among them are found the two with the highest rate. Nevertheless when they are left out, we still find that the low of 4.88 per cent is not much more than half of the high with 9 per cent and I think this is an encouraging fact. It suggests to one familiar with the local situation that even the best of the rates could be improved by a jealous guarding of the expectant mother. A not very flattering fact emerges when one notes that the average rate for the seventeen doctors is 7 per cent, while the average rate for the whole series is

TABLE III.

ANTE-NATAL DEATHS
THE CAUSES OF THESE HAVE BEEN CLASSIFIED AS FOLLOWS

I. Toxæmic	
(*a*) Syphilis	24
(*b*) Placental infarction	10
(*c*) Utero-placental apoplexy, ablatio placentæ	4
(*d*) Premature senility of the placenta	1
(*e*) Maternal glycosuria	1
(*f*) Eclamptic convulsions	6
(*g*) Drugs	–
II. Mechanical	
(*a*) Placental separation in prævia	2
(*b*) Placental separation from trauma	–
(*c*) Knots or torsion of umbilical cord	1
III. Developmental	
(*a*) One artery in cord (?)	1
(*b*) Small placental area	1
(*c*) General œdema of the fetus	1
(*d*) Other congenital anomalies	–
IV. Undetermined	8
	60

INTRA-NATAL DEATHS

I. Traumatic	
(*a*) Craniotomy	11
(*b*) Cerebral hæmorrhage	14
(*c*) Asphyxia	36
(*d*) Suprarenal hæmorrhage	1
(*e*) Other injuries	–
II. Infective	
(*a*) Pneumonia, present also in four others included under craniotomy	1
III. Toxæmic	
(*a*) Scopolo-morphine narcosis	–
IV. Developmental	4
V. Undetermined	–
	67

NEO-NATAL DEATHS

I. Traumatic		
Intra-natal	Cerebral hæmorrhage	18
	Suprarenal hæmorrhage	5
	Craniotomy (child breathed)	3
	Other injuries	4
Post-natal	Overlying	–
	Injury during artificial respiration	–
	Other injuries	1
II. Infective		
Ante-natal	Syphilis	11
Intra-natal	Pneumonia (5 stillborn)	1
Post-natal	Pneumonia	24
	Other infections	2
III. Toxæmic		
Necrosis of the liver		1
IV. Prematurity *per se*		18
V. Developmental		4
VI. Other conditions not peculiar to the newborn, *e.g.*, volvulus, gastro-enteritis, etc.		1
		93

6.51 per cent, accounted for by the absence of a neo-natal death among the 564 unattended by professional assistance.

To discover the answer to the question why are children stillborn, or why do they die soon after birth, there is only one certain line to follow and that is to autopsy a large number, and this has been done by several investigators. It is my purpose to present the result of such a study undertaken by Dr. F. J. Browne which has been reported in detail in the *Transactions of the Edinburgh Obstetrical Society*. It is felt that the information contained in the accompanying Tables has not received the recognition that it deserves, and that it will be helpful to call attention to certain outstanding features.

The light of such an investigation shines first on the disparity between his figures and ours relating to syphilis. Where he finds 35 out of 220 we report only 2 out of 453. Obviously we have passed over quite a number, even allowing for a lesser incidence in Ontario. It is stated that 1.7 per cent of the admissions to the public wards of the Toronto General Hospital for the year 1936 had positive Wassermann tests. At this rate there should have been 118 congenital syphilitics among our 6,954 births, or, on the other hand, 76 out of 453 if we had the same proportion as Browne. The correct figure would be known had all our mothers been tested, and it seems reasonable that this should be done. Even then we would not be as thorough as Browne, who demonstrated the spirochæte in the tissue in every case. Syphilis may be suspected, at any rate, when a stillborn baby is macerated and the liver and spleen and accompanying placenta are large and fibrous.

Next we are struck by the number of deaths following the heading "craniotomy", 4 for hydrocephalus and 10 when the infant was apparently normal. This terrible last resort is absent from our series, larger though it is, and this may be due to better physical development among Canadian women and to a more general use of Cæsarean section. At this point it might be helpful to pause and consider the experience of our small group of general practitioners with abdominal delivery. During this same period of eleven years 42 cases have been operated on in the two hospitals. There may have been a few more, since the records of one of the hospitals do not go back beyond 1931. However, taking this figure as a minimum, it indicates one baby out of every 166. The neo-natal mortality rate was very high, 21.4 per cent. Three of them died from the eclampsia of the mother, 2 because of the bleeding of placenta prævia, and the other 4, indefinite. The maternal mortality 4.76 per cent (both due to infection) may be compared with a general mortality for the 6,936 mothers who produced the 6,954 babies of 0.6 per cent. There were, by the way, 18 twins, 1:385. The improvement in neo-natal mortality shown by abdominal section over craniotomy is probably offset by the increased maternal mortality, and yet we are not sure that all of the mothers survived after craniotomy. Watson, from the Sloane Hospital for Women, recently called attention to what he states is a tenfold risk when a mother has an abdominal delivery, and further states that the chance of obtaining a living baby is not improved. Considering that the abdominal route is only chosen to escape a catastrophe it is hardly fair to compare these cases with normal ones.

Intracranial hæmorrhage claimed 16 per cent of Browne's series, and while this cannot always be diagnosed it may be suspected when the baby refuses to nurse, has a whining cry, convulsions and even coma. At post-mortem one often finds an extensive hæmorrhage from a venous sinus torn along with some dural fold, most commonly the free edge of the tentorium. When one considers the moulding of the head, compressed in one direction and elongated in another, and adds to this the violence necessary in certain deliveries one is not surprised that intracranial bleeding occurs. Browne finds it ten times commoner in breech deliveries, which he blames on haste in delivering the after-coming head, and we might suggest also on the compression of the body of the infant by the manœuvres of the obstetrician, bringing about over-distension of the thin-walled cerebral vessels. The lessened amount of elastic tissue in the vessels of premature infants explains the great liability they show to intracranial hæmorrhage, but it does not explain the bleeding that occurs when babies are born with membranes intact, or when they are delivered abdominally, and this not infrequently happens. For such reasons some maintain that congenital weakness in the walls of the cerebral vessels due to

maternal toxæmia is the primary cause of cerebral hæmorrhage of the newborn and violence is but secondary. As for delayed clotting- or bleeding-time Browne found it but twice in his series. We should not get the impression that all infants who suffer a cerebral hæmorrhage die of it. Ryberg followed for two years 49 babies who had shown definite evidence, and he found at the end of that time that 20 of them were idiots, 6 were intelligent epileptics, 2 had spastic symptoms, 7 had defects of the ocular muscles, 4 had died epileptic, and 10 were apparently normal children.

Hæmorrhage into the suprarenal capsule may be mistaken for pneumonia, because of the very high temperature and rapid respiration. It is responsible for from 3 to 5 per cent of neo-natal deaths.

Asphyxia, due to knots in the cord, compression of the cord, insufficiency of the placental circulation, or even excessive uterine contractions, is the commonest cause of intra-natal death. For any such reason the child begins to breathe *in utero*, with the result that at post-mortem examination one finds the lungs filled with liquor amnii, epidermal scales and vernix caseosa. Careful clearing of the airway while the newborn child is held suspended head down may be sufficient to save a small proportion of them, and a warning should be given against vigorous efforts at resuscitation in cases of asphyxia pallida, which is often a symptom of intracranial damage. Gentleness and the use of 5 per cent carbon dioxide in oxygen in a respirator, such as Drinker's, is recommended by Kugelmass.

Pneumonia caused 25 of the deaths in Browne's series. This is not the usual blood-borne disease but an inhalation pneumonia due to infected mucus or liquor amnii. The organism is seldom the pneumococcus, but generally the staphylococcus, streptococcus, or a bacillus. Johnson and Meyer found evidence of such a pneumonia in 19.4 per cent of 500 autopsies.

While one may well be critical when prematurity is given as the only cause of death for 146 out of 453 cases, still, as Browne points out, it is the primary cause for about 10 per cent. Among them he includes twins born before viability, prematures due to placental hæmorrhage, or infants born after induced labour. Another study of this problem showed that all infants under 1,200 g. died, no matter how long they had been intra-uterine. Of those between 1,200 and 2,200 g. only 69 per cent left the hospital alive and some of them died soon afterwards. If they survived to the end of a year their chance of living was not less than that of children born at term. Finally, when they reached the age of five or six they had recovered normal weight and were just as bright as full-term children.

In conclusion, it may be said that if this paper has engaged the reader's attention he will in future hesitate before using such questionable terms as debility, inanition, convulsions, still-birth or prematurity in certifying to the death of the newborn. Even atelectasis should not be used, as it is often physiological or secondary to some other real cause of death. An intelligent appreciation of the information conveyed by Dr. Browne's charts will do much to improve the vital statistics along this particular line. But they can be of much greater use to us in the matter of prevention. Better pre-natal supervision will reduce stillbirths by 50 per cent. The recognition and treatment of syphilis in the early months of pregnancy is something that there is no excuse for neglecting. Wassermann tests should be taken routinely on all women in the early months of pregnancy. Careful physical examination before term will indicate the abnormal case and allow time for planning the most appropriate method of delivery. In carefully selected cases there is no doubt that it is wiser to run the risk of an abdominal delivery, which in experienced hands is better than presenting the parents with a potential idiot dragged through a narrow pelvis by forceps. We should bear in mind the greater risk to the child in breech delivery and in these cases as well as in premature births it were well to practise the intramuscular injection of parent's blood, which some advocate to limit the extent of cerebral hæmorrhage. Hospitals should all be provided with efficient but not necessarily expensive equipment for the care of prematures and the administration of oxygen and carbon dioxide.

Of the 453 neo-natal deaths in Sault Ste. Marie in these 11 years, none occurred in the families of the doctors themselves. This may be just accidental, but as long ago as 1914

Stevenson was quoted in the *British Medical Journal* as showing that when the infant mortality in the families of unskilled labourers was 152 per 1,000 legitimate births, and in the middle class generally was 61, it was only 39 among the families of the medical practitioners, and this was the lowest figure of all. What we can do for ourselves we can do for others.

DERMATOLOGICAL NEUROSIS*

BY W. R. JAFFREY

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A DISCUSSION of the effect of psychological injuries and emotional strain in the production of cutaneous disease would involve a very long paper, but some of the more evident instances where the psychoneurosis complicates a condition already present are very prominent in every day consultations.

The designation "neurodermatosis" includes, generalized pruritus, localized pruritus (pruritus ani, pruritus vulvæ, pruritus of the scalp, lichen simplex chronicus), dyshidrosis, urticaria, angioneurotic œdema, neurotic excoriation or picker's disease, alopecia areata, and even some types of rosacea.

The general signs and symptoms these patients may present are: easy fatigability, nervous irritability or depression, gastro-intestinal disturbances, migraine type of headache, and other obscure symptoms, and although organic disease may be found in association the large majority show no organic disturbance.

Perhaps the most aggravating to the physician and the most difficult to handle are the neuro-complications of a dermatitis due to an external irritant, including occupational dermatoses, and along with them must be discussed the all too frequent dermatid which must be differentiated from the original dermatitis: (1) dermatid — secondary toxic eruptions and ostiofollicular furuncle; (2) neurodermatitis, neuro-instability, protoplasmic instability and perverted fatigue; (3) artefacts, malingering. These three distinct types of complicating reactions are seen in association with cases of dermatitis ascribed to external irritants contacted during occupation.

1. The dermatids are most common in cases of chronic dermatitis which show some localization and are often an explosive result of overtreatment of the original lesion. These are the most serious reactions associated with external irritant dermatitis and are secondary toxic eruptions. A patient develops a primary dermatitis and absorbs material from broken-down cells in the original area. This material is carried by the blood stream to distant parts of the body and a secondary eruption is produced, often largely an erythema, although it may vary in type and even be similar to the original eruption. This occurs usually in the subacute stage. A plausible explanation is, that, due to the allergic phenomenon taking place in the epidermal cells of the skin, some allergic substance is set free which at once goes about setting up a cellular or protoplasmic sensitivity of epidermal cells throughout the body, and when the protein, or whatever the material may be called, of degenerating epidermal cells in the area of dermatitis gets into the circulation in sufficient amounts an explosion takes place which may have focal or general distribution. With dermatophytids where the fungus toxin is the activator often this reaction originating from the feet may affect the hands only. Scalp tinea may originate a dermatophytid on the back and shoulders, especially following such treatment as epilation.

2. The neurodermatoses sometimes are designated to include that type which is portrayed by the lichen simplex chronicus group. A more liberal conception of these cases will place all those of the neuro-instability and perverted fatigue type under this classification. These cases are very common, very aggravating to the patient, and a constant source of worry to the physician and the cause of much friction with compensation authorities. They present a chronic dermatitis with considerable lichenification and marked localization, occurring on the hands, forearms, upper arms, axillæ, around the neck and shoulders, on the legs and feet, and sometimes the face or scalp. This has to be

* Read before the Academy of Medicine, Toronto, April 6, 1937.

differentiated from a frank seborrhœal dermatitis, which usually commences on the scalp and around the ears and spreads to the chest and shoulders.

Although the erythema followed by œdema, which is the ordinary lesion, is started by some irritant it very soon becomes purely an artefact and often sufficient artificial rubbing and scratching allows all sorts of other substances easy entry to the eroded epidermis, and if a sensitivity does not exist already the inoculation soon produces the phenomenon of *allergy* or *atopy*.

3. This type or reaction must not be confused with the artefact produced by the malingerer or that of the psycho-neurotic who produces these lesions for reasons which he himself does not comprehend. These may be for the purpose of getting sympathy, of self-punishment, or are the expression of some religious or sexual perversion. Most of these types of patients will no doubt exhibit the anæsthetic syndrome and are described by O'Donovan as "glib". These patients are long-winded—knee jerks—very glib, extended hands very shaky, the palate and cornea insensitive to touch and the skin to pinprick. The basis of these very different reactions is a protoplasmic instability with which the patient is born. No doubt the primary explosion is due to a special affront suffered by contact, inhalation or ingestion, during the occupational exposure. In a great many of these the patch test may elicit the cause. Scratch testing is not recommended and it must be borne in mind that a positive test only is of value. Great care must be taken in handling these cases which develop dermatitis, and one is ill advised to make use of tests for allergy during the attack.

There are a few principles to be followed in the care of these patients suffering with neurodermatitis. Those of compensation character are likely to get an idea that the continued duration of a dermatitis is surely due to the original cause, and some will spend a great deal of time endeavouring to get their proper rights, as they see it. Some will be seen who as long as a year after their original trouble are still seeing doctors, visiting and writing the compensation authorities to have their case reviewed, and seeking the aid of lawyers to get redress, and it is notable that when they think their case is going favourably their trouble will be at its worst. As soon as they have what they think is redress, no matter how temporary the compensation authorities mean it to be, they suddenly improve and have a set-back as soon as they see the wind blowing the other way or think they have not had sufficient consideration. The psychological attitude of these patients should be guided skilfully or they are very troublesome.

The malingerer with an artefact is much smarter and has to be handled very carefully, but the lesions are usually on accessible portions of the body and may vary so much as to simulate many known conditions, but have not the definite characteristics of any.

Those patients of the perverted fatigue type usually present the simple neurodermite or the dyshidrotic types of lesions, and are not looking for pity so much as alleviation of their trouble. They go to doctor after doctor, have their tonsils and teeth out, are put on diets, and given laboratory examinations and x-rayed, where a careful study of their daily life and associations will find them mentally tired and with some worry which is probably real, and relief from the strain is more help to them than all the foregoing. This is perverted fatigue.

The patient who develops neurodermatitis becomes a chronic dermatitis case, belongs to the group of dermatological neuroses, and exhibits a definite neuro-instability, and the skin manifestation is really nothing more than the explosion point of nervous-mental exhaustion or perverted fatigue. The phenomenal recovery of some of these cases matches the obscurity of the etiology, and should make us more cognizant of the skin as a shock organ for mental explosions.

RADIOLOGICAL EDUCATION*

BY W. A. JONES, M.D., F.R.C.P.(C.)

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IN a broad sense the term "medical radiology" refers to the application of all types of radiation in the diagnosis and treatment of disease. It means, in a more restricted sense, the use of x-rays and radioactive substances in medical diagnosis and therapy. Beginning with the discovery of x-rays by Roentgen in the latter part of 1895, it has grown through a period of forty-two years with gradually increasing vigour, until now it has assumed the position of one of the widest and most difficult fields in the practice of medicine.

In the early days x-rays were used in diagnosis by almost any person with a mechanical bent or scientific curiosity who possessed the means of acquiring an x-ray apparatus. Physicists, photographers, physicians, and amateur experimenters of all types played with the new toy, and began those first stumbling attempts to investigate human anatomy and disease. Many of them paid dearly for their temerity in launching out into this new sea of investigation, and maimed hands, scarred faces, and loss of limb and life were their reward. These early investigators learned by trial and error. They widened their concepts of the new science by experimentation, and by checking their diagnoses at the operating table and in the autopsy room. Organized teaching of the subject lay many years in the future. Personal contact with their colleagues at the expense of many miles of travel and the reading of the meagre literature of the day constituted their only means of acquiring knowledge of the new subject.

The new science of radiology soon began to develop along two rather distinct lines. The physicist, the x-ray engineer, and the x-ray technician became responsible for the manufacturing and technical side of the work, while the medical man, with technical training in x-rays and with his background of general medicine, surgery and the basic medical sciences, became the interpreter and director of this field of medicine. The transition to this stage of development has been very gradual, and in so far as Canada is concerned it is only within the last fifteen years that the concept of the radiologist as a physician has become general amongst the laity, or, for that matter, amongst the profession. Indeed, even at this date there is seen in many of the smaller hospitals and a few of the cities the anachronism of the lay technician interpreting films and doing fluoroscopic examinations. Army x-ray training during the Great War was probably the first step taken by Canadians to train physicians in radiology. Since that time many young medical men of this country have had training as interns in the radiological departments of the larger hospitals in Canada and the United States, and in Toronto a few medical graduates have obtained the Diploma of Radiology. There are, however, too many who take short courses of one to six months in this important specialty and who then blossom out in their own communities as full-fledged radiologists. This is not only unfair to the public but it is also a source of embarrassment and heart-burning to the medical man himself who takes this short cut to his chosen field of work. It is not, however, altogether the fault of the man chiefly concerned in this matter, but the responsibility lies at the doorstep of the medical profession as a whole and radiologists in particular, in that we do not all advise and insist upon a proper standard of training before such a person is allowed to be labeled as a radiologist. There was a time in the past when short periods of training and self-teaching by books and experience were necessary. That time, however, is now long past. The field is too broad and the work too complicated for any ordinary person to master this specialty without a long and controlled period of training. The opportunities for training are now available and the need for training is very evident. Under-graduate radiological teaching is being carried out now as part of the medical

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course at the various universities. The idea underlying the teaching of radiology to the medical student is to acquaint him with the possibilities for the use of x-rays and other sources of radiant energy in the diagnosis and treatment of disease. He is familiarized with such from a general point of view so that he may properly assess the value of these methods and appreciate intelligently the interpretation of films. The time given to the teaching of radiology in a general medical course is far too short to allow the student to attain enough information to enable him to practise radiology. If the student after he graduates desires to practise this specialty he has much to learn.

In outlining what might be considered a suitable standard of training and qualification for radiologists one must be guided by the recent trend of events in Britain and in the United States. In Britain the British Association of Radiologists, and in the United States the American Board of Radiology have both formulated very similar plans for dealing with such matters. What is proposed here naturally follows the lead of our confrères in these countries. Their standard is high and we need not improve on it. It is perhaps unnecessary to add that we must not lower the level of our standard. It is also right and proper that our standard should be such as is acceptable in both these countries, so as to allow the free interchange of radiologists across international boundaries.

An aspirant to the specialty of radiology should be first of all a medical practitioner legally qualified in the country in which he practises. He should have had at least one year of service as a general intern in a recognized hospital. More general work, part of it in general practice, would be desirable. He should be a man with the knack of getting along well with his fellow practitioners, and he should be capable of obtaining the confidence of his confrères. He should be (remember that we are not necessarily talking about facts as they are but of an ideal which we should strive to attain) above the average grade of intelligence, and should have a good general knowledge of medicine and surgery. Having then these requirements, there follows a period of training. In detail the type of training is debatable, but in general he should have:

1. One year of instruction, study and practical work in radiographic anatomy, radiobiology, radiophysics, radiological technique and pathology. During this period he should also serve in a recognized radiological department, studying radiographic diagnosis and radiotherapy.
2. Two further years of training in a recognized department of radiology.
3. During this period of three years he should also familiarize himself with the general medical and surgical procedures centring around those diseases which he will be called upon to diagnose and treat radiologically.
4. Two further years of training or practice.
5. Examinations during and/or at the completion of this period of training.

All of this may seem like an unduly long period of training and intensive study, but when one realizes the rapidly expanding field of this specialty and the fundamental necessity for study of the basic sciences and for practical work it will be recognized that such a period of time will be fully occupied.

One of the criticisms levelled at the granting of diplomas in radiology by the universities is that at present the accent is placed rather too strongly on physics and not enough on practical radiological training. One of the reasons for this is the short period of time (eight to twelve months) required for the courses. Queen's University has endeavoured to overcome this drawback, and for the recently created diploma in medical radiology requires one year at the university and two further years of "field work" in a recognized radiological department.

There is a demand in Canada now for competent radiologists. The demand is growing. There are half a hundred or more small communities requiring the services of travelling radiologists in order that the public and the medical profession generally should have placed at their disposal proper radiological service. When one considers the so universal application of radiology to diagnosis and its wide use as a therapeutic method it seems almost unnecessary to stress the value of the trained radiologist to the community. Yet it is too true that, except in the large cities, expert services of this type are available to only a small portion of the Dominion. One can readily comprehend the usefulness of such a radiologist in the small community, a specialist well trained as a radiological consultant, one who is not in direct competition with the other medical men of the district, one to whom the practitioner can refer his cases in perfect confidence, a man who knows

the uses and abuses of his particular methods of diagnosis and treatment, and who merits the confidence placed in him.

Such a man would be heartily welcome to his confrères, and would prove a most useful addition to the community. He would occupy a position which unfortunately is not now filled in too many places in this country and others. It is the duty of the profession to see that men are trained to perform this service satisfactorily.

TREATMENT OF GONORRHŒA BY HYPERPYREXIA IN GENERAL PRACTICE

BY W. H. AVERY, M.D.

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THE series of 18 treatments given for gonorrhœa were, I must confess, all in the nature of experiments. The experience gained was considerable. They were all conducted on a trial and error basis; we learned about the subject as we went along. Having seen a number of cases treated by various methods of hyperpyrexia in New York and Chicago, and having several cases of chronic gonorrhœa not doing well in my own practice, I decided to try out the method.*

The two principal methods of raising temperature in vogue at the present time are as follows. The air-conditioned cabinet was brought out by Kettering and Sittler, of the General Motors, in which air at 150 to 160° F. is circulated about the patient, with a humidity of 50 to 75 per cent. This method depends on driving heat into the body from the outside, and it is said that the high skin temperature produces a pulse rate of 20 to 30 beats a minute higher than the other cabinet method, in which the temperature of the cabinet is maintained at 100 to 110°, but the heat is generated in the patient's body by an electro-magnetic current such as the General Electric Inductotherm generates. The patient is said to be more comfortable in the low temperature cabinet. This latter apparatus is the one we use.

The cabinet contains two mattresses. The patient lies on the upper one and the cable from the inductotherm passes between the two mattresses, each mattress being about two and one-half inches thick. The cabinet is heated to betweent 105 to 110° F., before the patient goes in.

A number of writers maintain that this is strictly a hospital treatment, but there are others who hold that the treatment can be carried out satisfactorily in office practice. With one or two graduate nurses and the constant attention of the doctor I see no reason why the treatment cannot be given in an office, which, of course, must have adequate room and facilities. I think a great deal depends on intelligent nursing while the patient is in the cabinet. These high temperatures will not be induced lightly by any doctor. Undoubtedly one feels while watching these patients subjected to prolonged high temperatures that definite risks are involved, and some of the danger signals may not be fully understood. One has the same apprehension when giving his first anæsthetic. I know there have been fatalities in private practice in the United States which are not reported in medical literature, but, on the other hand, Potter treated over 800 and Neymann, of Chicago, over 1,000 cases with hyperpyrexia with no mortality. Neymann (quoted in Potter's article) says that one can maintain temperatures up to 106° F. for five, six, seven and eight hours, with comparative ease and without taking a great risk. He speaks now of the low-temperature cabinet, a cabinet which in itself will not produce pyrexia at all, but simply serves as a sort of blanket in which the patient can move freely. With this sort of apparatus patients in advanced stages of diabetes, with organic heart disease, with advanced arteriosclerosis, with diseases of the liver and the like, have been and are being treated, and the death rate remains virtually nil in over one thousand cases. This may be true, but I, for one, would certainly not care to take any such responsibility in office practice.

The contraindications for hyperpyrexia, as outlined by Owens, are as follows—advanced

* I am greatly indebted to Prof. Clarence A. Neymann, of Northwestern University, Chicago, who is the originator of fever treatment and original research worker in the hyperpyrexia field. He kindly demonstrated his technique and gave me every opportunity to familiarize myself with it. His technique is the one I use.

vascular and renal changes, cardiac weakness, chronic debilitating diseases, chronic alcoholism, and marked nervous and emotional instability. It is to be noted, however, that such conditions, with the exception of alcoholism, are not commonly associated in patients who contract gonococcic infections.

Potter's laboratory findings in hyperpyrexia are as follows. "During fever heat a leukocytosis occurs; there is a drop in the sedimentation-test reading; during fever therapy the systolic pressure drops 20 to 30 points, and the diastolic during height of the fever often drops to zero. There is a great loss of chlorides, which have to be replaced by giving normal salt solution by mouth. Because of the piling up of sodium in the system there is a tendency to an alkalosis; therefore, fruit juices are contraindicated during treatment."

The procedure we have adopted is as follows. A history is taken (positive slides for gonococci had been obtained previously by us or the patient's doctor). A careful physical examination is made, including urinalysis and blood pressure. Basal metabolism tests and electrocardiograms are not done.

Potter says the two following tests are especially useful in evaluating the behaviour of the circulatory and nervous systems under hyperpyrexia: (1) the exercise test, to determine how quickly the pulse will return to its normal rate after exercise; (2) the cold pressor test for early diagnosis of essential hypertension. These tests were made. The patients were also given 1½ gr. of nembutal. Some of the more nervous ones had full doses of bromides a day or two previously.

The nature of the treatment is explained to the patient. We tell him that we expect him to cooperate with us, that he may be very uncomfortable at times, but we expect him to stick it out, that he will never be left alone a minute while in the cabinet, and that on the slightest indication of danger he will be taken out. We try to get his confidence. The patient is then placed in the cabinet, which has been pre-heated to 110° F., and the inductotherm is turned on. Ice-cold towels are placed on his forehead and the breeze from a fan is directed on his face. We try to prevent the taking of large quantities of cold fluids before high temperatures have been reached unless the patient insists. We give small quantities of physiological solution of sodium chloride at room temperature. If the patient objects to the salt solution we disguise the salt in other beverages. The most trying time for the patient is when the temperature is going up. We want this time to be as short as possible, as under good circumstances it usually takes us two and one-half hours to get him to 106° F. (rectal). To allay apprehension and nervousness during this period we gave pantopon or morphia, and could notice no difference in the efficiency of the drugs. We rather prefer morphia. These sedatives may have to be repeated later on in the treatment if the patient gets very restless.

The rectal temperature and the pulse of the patient are recorded every fifteen minutes while in the cabinet. Taking the rectal temperature is very essential. In the first few treatments we relied on mouth temperatures, and as the patient had cold towels and the fan on his face, together with frequent cold drinks, we have reason to believe mouth temperatures were far from accurate. During our fourth experiment with the treatment the patient exhibited some delirium. The nurses were taking mouth temperatures. I decided to take the temperature rectally, and found it to be 109.6° F. Needless to say, we cooled him off and put him to bed. He was brought back in five days, completed seven hours' hyperpyrexia between 106 to 107° F. (rectal) which cured him.

Some authorities advocate protection for the extremities, such as cotton stockings, as the touching of wet skin surfaces tends to draw sparks and burn the patient. We did not do this, and one patient's right heel made slight contact with his left instep over a period of time, causing a burn, quite severe but small in area. Precaution was exercised after this to keep the limbs apart when the patient was asleep. If we should have more burns we would allow the patients to keep their socks on. We tried to keep the temperature between 106 and 107° F. (rectal). Any temperature exceeding 107° was immediately reduced by turning off the inductotherm, opening the cabinet, giving the patient a sponge bath, and, if necessary, an ice-cold enema.

Our highest pulse rate in this small series was 160, which was in our first case, second treatment. The mouth temperature was 107°,

but in the light of later events I have reason to believe it was much higher. We cooled this patient out at 106°; his pulse dropped to 130 and rose again to 140, at which time he had completed six hours of mouth temperature registering 106° F. These recorded temperatures were far from accurate, and I believe they ran much higher.

The patients were allowed light breakfasts on the morning of the treatment, and so far we have seen no nausea that could not have been attributed to the sedatives. One or two were slightly nauseated for a time while the temperature was rising.

The pulse rate during treatments was usually around 130 to 140; occasionally, between 140 to 150. The patients whose pulse rate approached 150 were watched very carefully, and as we only had two treatments where the pulse rate exceeded 150 we came to the conclusion (which may be erroneous), that we were in, if not a danger zone, at least one where the patient required the utmost care, and we were rather inclined to lower the temperature in order to reduce the pulse rate. We were also guided by other symptoms, such as colour, as to whether the patient was embarrassed or not in breathing, and the clarity of the mental processes. Most of them for a short period at a time were slightly delirious, but would give a clear enough answer when asked a direct question. If at any time the patient had remained confused and had not been able to answer questions intelligently, we think we would have discontinued the high temperature and brought him to a lower level.

All of the patients acted very well, which was due to a great extent to tact and diplomacy on the part of the nurses. A great deal of attention is demanded, such as position of the fan, arranging of pillows, position of the head, care to the eyes and face, and general comfort.

CASE 1

Mr. V., 20 years old, treated on October 31, 1936. There was a history of previous infection in 1933; the present infection began in May, 1936. He had been treated by corbus ferry vaccine, permanganate irrigations, argyrol instillations, prostatic massages, etc. The second urine (two-glass test) contained shreds and urethral morning secretions, positive for gonococci. He was rather discouraged with the treatment and decided to try hyperpyrexia. He was placed in the cabinet at 9.45 a.m.; at 10.45 his temperature was 104° F. (oral); at 11.25, 106° F.; at 12.30, 107.2°, and his pulse rate reached 155. He became quite delirious and insisted he was dying. I have no doubt his temperature was higher than 107° and should not have been taken by mouth. We cooled him down to 106° and he was still delirious. We decided to cool him out and brought his temperature down to normal by 3.30 p.m. He became rational at 104°, and his pulse came down accordingly; of good volume and regular. He slept three hours and went home. His urethral smears remained positive and we placed him in the cabinet again on November 4th. The second time we gave him very little fluid, and we were much slower in getting his temperature to 106°. We held him five hours at temperatures over 105°, ranging as high as 107°; he was not delirious, but his pulse from 1.45 to 2.15 p.m. ranged as high as 160. I feel these mouth temperatures were more accurate than those of the previous treatment, on account of his taking little or no cold fluid. They were probably a little higher than recorded. His temperature was normal at 5.45. He slept three hours and went home by taxi. He did not go to work the following day but resumed his occupation the next day. He had no urethral discharge, no shreds in his urine, and was apparently cured. Over a period of two months various provocative tests were made with no results. He has remained well since.

CASE 2

Mr. A., 50 years old, with no history of previous infection. Present infection came under chemical treatment November 1, 1936. There was profuse discharge and he complained of considerable pain on passing urine. He had a long tight foreskin. No local treatment was instituted beyond sedative rectal suppositories, with full doses of potassium citrate and tincture of hyocyamus by mouth. Rest in bed was advised. This he followed for a few days and was considerably better of his more distressing symptoms. His business suddenly necessitated a long motor trip of some 300 miles, which he did in one day without my permission. He came to see me the following day very distressed and all his symptoms more acute. We decided on hyperpyrexia and the treatment proved spectacular in its results.

He was placed in the cabinet at 9.30 a.m. His temperature as recorded by mouth was 99° F.; at 11.00 a.m., temperature 102° F.; at 11.45 a.m., 105° F.; at 11.50, 106°. We were still taking mouth temperatures, and I feel that these temperatures were not accurate, no doubt due to frequent drinks of cold fluid. At 12.15 his temperature was 106° by mouth and he was slightly delirious. His pulse, as noted on his chart, never went above 120. He was cooled down to 105° and was held on about that level or slightly over until 4.00 p.m. He insisted at this point that he had to be taken out of the cabinet, that he had had enough treatment. We considered it inadequate, but as he insisted we opened up the cabinet and cooled him out. He was put to bed after drinking a pint of milk. He slept for two hours and then got up of his own accord and went to the toilet to urinate. He was completely free of all symptoms which was very gratifying to him. He was full of praise for the treatment but we were disappointed as we considered he had not had enough fever. His brother called for him and drove him home. He remained in bed the following day. He reported to my office the following day. He had no urethral discharge, but his urine contained a few shreds. Centrifuged smears showed no gonococci. A few days later his urine was clear of all shreds. He has remained free of any symptoms since.

CASE 3

Mr. B., 47 years old, referred by Dr. McC. There was no history of previous infection. He drank considerably. He was hard to manage in so far as treatment was concerned. He had been under chemical treatment for three months. He was placed in the cabinet on December 1st, at 9.45 a.m., temperature

97.6°; at 10.45 temperature 104°; at 11.30, 105°; at 12.15, 107°; 12.30, 107°; 12.45, 107°; becoming quite delirious. The nurses had been taking these temperaures by mouth. I decided to open the cabinet and take the temperature rectally, and to my astonishment and consternation the thermometer registered 109.6°. Not believing the thermometer, I shook it down and took it for another minute. It again registered 109.6°, and his pulse was 160. The inductotherm was turned off, the cabinet opened full length, a wet cold sheet placed on the patient, and the breeze of the fan directed into the cabinet. His temperature dropped rapidly and we cooled him out to normal and put him to bed. He slept a few hours and went home. He developed a mild prostatitis and was kept in bed three or four days. Placed in the cabinet again on December 8th, and his rectal temperature 106° F., was maintained from 1.30 to 8.30. At 8.30 he was cooled out and was put to bed at 9.30. He said he was hungry and received two slices of buttered toast and a quart of milk. He slept all night and in the morning ate a hearty breakfast and went to business. Several days later his doctor reported shreds in his urine and gonococci in the centrifuged specimen. He now developed a mild epididymitis and spent three or four days in bed. He resumed his business for four or five days and came back for more treatment on December 22nd. He was placed in the cabinet for the third treatment at 9.00 a.m. His rectal temperature at 12.45 was 106°. This was maintained until 6.30 p.m. at which time he was cooled out. He went home that night. The thickness in his epididymis was gone and he was free of symptoms. His doctor kept him under observation for a month and pronounced him cured.

CASE 4

Mr. H., 23 years old, referred by Dr. M. on December 28th. He had been under chemical treatment for three months. The morning meatal secretion was positive for gonococci. He was placed in the cabinet at 9.00 a.m. His temperature reached 105° at 11.00 a.m. and was held between 105 and 107° until 6.15 p.m. at which time the treatment was discontinued. He slept for one hour, had nourishment, and went home. His pulse was between 140 and 150 the greater part of the time. His doctor kept him under observation for a month and reported that he was cured.

CASE 5

Mr. Mac., 47 years old, referred by Dr. H. on March 10th. This case was of long standing. He gave a history of being infected in 1922, at which time he had treatment but was not cured. He had quiescent periods when there was no discharge. After drinking bouts the discharge would return. He admitted no fresh infection. Slides made on different occasions were positive for gonococci. He was placed in the cabinet at 9.30 a.m. and by 12.00 his temperature was 105° rectally; by 3.00 p.m., 107° rectally. His pulse at this time was over 150, he was cooled out slightly and held between 106 and 107° until 7.30 p.m. at which time he was cooled out. His doctor has been keeping him under observation and so far there has been no return of symptoms.

Five other cases treated were rendered symptomless. Three have been under observation for two months without return of any symptoms; the two other cases were lost track of and no follow-up was available.

In this small series the patients did not exhibit any very alarming symptoms while in the cabinet. We did not have to resort to any so-called emergency treatment. The only alarming temperature was in our second case, which was our own fault. The patient was readily cooled out by opening the cabinet and putting on cold wet sheets. The nurses keep on hand an oxygen tank, hypodermics of full doses of caffein, coramine and adrenalin. Intravenous sugar solutions are instantly available, also an enema can filled with ice water, and of course the cabinet must be so constructed that its influence as an insulation can be instantly removed from the patient.

THE TREATMENT OF EPILEPSY IN CHILDREN*

BY H. M. KEITH

Montreal

DURING the past two decades considerable evidence has accumulated to indicate that chemical changes within the body are intimately concerned in epileptic attacks. The work was stimulated by the announcement, shortly after the war, by Conklin, of Battle Creek, that starvation for a period of about two weeks was a useful treatment for an epileptic patient. It was thought possible that the disturbance in acid-base balance was responsible for this beneficial effect. In 1921, Wilder,[1] at the Mayo Clinic, suggested that the ketone bodies produced during starvation were responsible for it. To prolong this effect of starvation, he then suggested the use of a diet that was high in fat and would produce ketone bodies in the urine.

While studying the effect of ketone metabolism in epileptic children, McQuarrie[2] felt that the water metabolism was of more importance than the presence or absence of ketone bodies themselves. The importance of water was emphasized at the same time by Fay,[3] who studied patients from a surgical point of view.

Jarloev,[4] in 1921, reported that the pH of the blood tended to be high preceding epileptic convulsions. Geyelin *et al.*[5] stated that there

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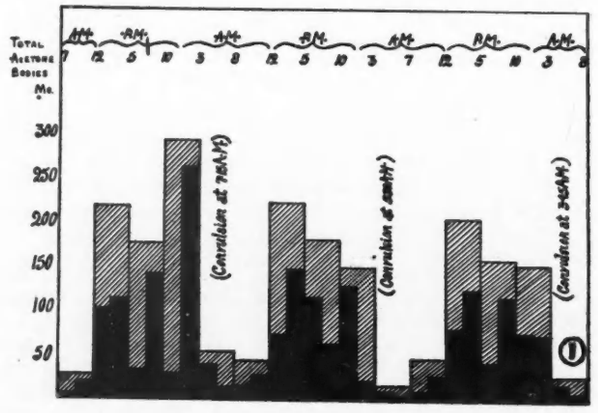
* A paper read at the sixty-eighth Annual Meeting of the Canadian Medical Association, Ottawa, Section of Pædiatrics, June 23, 1937.

From the Montreal Neurological Institute.

was no pH curve definitely characteristic of epilepsy, but that the blood of epileptics showed a distinctly wider range of pH from day to day and from hour to hour than did the blood of normal persons. Marrack and Thacker,[6] on the other hand, stated that the blood pH in epileptic patients was in the same range as in normal controls. In 1921, McQuarrie and Keith[7] studied the blood pH in relation to the excretion of acetone bodies and total acids, etc., in several epileptic children. If the normal pH of the blood was considered to range from 7.33 to 7.42, the seizures, in this patient at least, were much more frequent when the pH of the blood tended to be toward the alkaline side.[7] Moreover by giving this patient, who was under the influence of a ketogenic diet and not having any convulsive attacks, 10 grams of sodium bicarbonate over a period of a few hours, several epileptic attacks were precipitated as the pH of the blood changed from 7.33 to 7.65. This patient was a girl of twelve years of age having many attacks, and in studying other children with fewer attacks it was found that this relationship was not always present. At the same time, a careful study was made of the excretion of acetone bodies in the urine of several children having epileptic attacks. These children, on a ketogenic diet, had a definite curve of excretion of acetone bodies.[8] It was felt significant that convulsions occurred in the early morning when the excretion of acetone bodies was at a minimum, as can be seen in Chart 1. This fitted in well with the suggestion of Wilder that the mildly anæsthetic property of diacetic acid and acetone was the factor preventing convulsions. In an attempt to prove whether this was so the present author performed a number of experiments on rabbits.[9] He found that the injection of a definite small amount of thujone, the active principal of oil of absinthe, would invariably produce a convulsion in a rabbit when that rabbit was injected for the first time. Accordingly, he injected intravenously a known amount of diacetic acid, acetone, and beta-hydroxybutyric acid as well as other substances. Rabbits were used in groups of six or more, and it was shown that diacetic acid and its sodium salt had a pronounced anti-convulsive effect. Other substances, it is true, had some anti-convulsive effect, but with the exception of sodium-phenobarbital, the aceto-acetic acid and its sodium salt were the most active. Unfortunately this substance is so unstable that it cannot be given by mouth. Aceto-acetic acid, however, can be produced in large amounts by means of a ketogenic diet, and this is an efficient method in treating certain patients, particularly children.

Ketone bodies have, however, another effect upon the body tissues, namely, partial dehydration. McQuarrie[2] felt that this might be an important factor, and was able to show in certain epileptic children that the administration of large amounts of water combined with the injection of pituitrin produced attacks and that the reduction in the water intake to a minimum decreased attacks or caused them to disappear. (Chart 2). This is in line with studies of



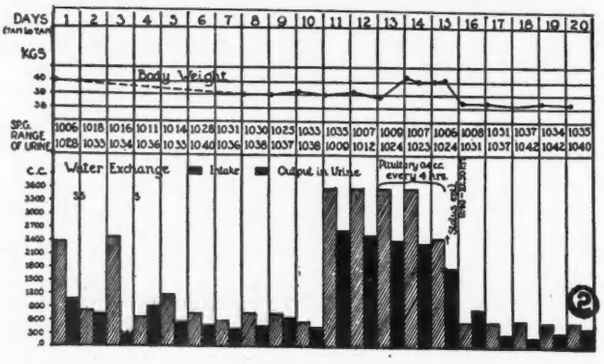


Chart 1.—Time relationship between occurrence of convulsions and minimum degree of ketosis as shown over a period of three days. Gradually diminishing ketosis due to excessive caloric value of diet in M.P., an epileptic girl, aged 12, weighing 36 kg. Diet (started on previous day): protein, 44 g.; carbohydrate, 44 g.; fat, 252 g. (From McQuarrie, I. and Keith, H. M., ref. 8.)

Chart 2.—Relationship of seizures (S) to the variations in the water exchange produced by restriction of water and forcing of water; also effect of solution of pituitary in connection with the forcing of water in E.M., a girl, aged 10 years. A borderline, nonketogenic diet containing 50 g. each of protein and carbohydrate and 130 g. of fat was employed. Status epilepticus was controlled by use of chloroform after fifty minutes. (From McQuarrie, I., ref. 2.)

Rowntree[10] and his co-workers published a few years previously. They showed that convulsions could be produced by the oral administration of large amounts of water, with or without the subcutaneous injection of pituitrin. McQuarrie suggested that there was a disturbance in the regulation of water exchange, with possible hydration of the brain tissues. Again, by using rabbits, the present author was able to show that this was indeed so.[11] Large amounts of water by stomach tube accompanied by repeated injections of pitressin did cause a swelling of the brain tissues and an increase in the animal's susceptibility to convulsive attacks.

TABLE I.

Substances given	*Amount c.c.*	*Total number of animals*	*Number with spontaneous convulsions*	*Thujone, c.c. per kg.*	*With convulsions*		*Brain solids per cent*
					Number	*Per cent*	
Pitressin (subcutaneously).....	0.1	7	7	0.2	6	85.7	19.81 ±0.24
Distilled water (by stomach tube).	180-500						
Pitressin (subcutaneously), 10 doses	0.1	8	0	0.2	3	37.5	21.3 ±0.21
Hypotonic saline solution (0.45 per cent intravenously).....	150-500	13	0	0.2	2	15.7	19.7 ±0.14
Distilled water (by stomach tube).	560-850	6	2	0.2	4	66.8	19.4
Controls (43 rabbits).....	....	..	..	....	..	....	21.6 ±0.07

However, it is interesting to note that œdema of the brain, produced by the injection of hypotonic salt solution but without the injection of pitressin, did not increase in any degree the rabbit's susceptibility to convulsions. This would indicate that swelling of the brain itself is not the important factor, and it is now thought that the interchange of salts between the cells and the blood stream may be still more important.

As above stated it has been found that a ketogenic diet, producing large amounts of diacetic acid in the urine, is a satisfactory method of treatment, particularly in children. Some few years ago, Helmholz and Keith[12] summarized the result of such treatment in a group of children followed for periods from one to ten years. All these children were treated at the Mayo Clinic.

One hundred and sixty patients were treated satisfactorily over a period from one to nine years. Of these, 36 per cent remained entirely free from attacks of any type so far as is known to themselves or to their parents; 21 per cent were improved, having only an occasional attack; 43 per cent were not benefited, although they carried out instructions fully. We may say, then, that with the ketogenic diet alone one-third of the epileptic children can be made free from seizures and 50 to 60 per cent can be improved. This percentage of so-called cures could undoubtedly be increased by a more refined method of diagnosis. Eley,[13] showed that when children were subjected to encephalography 90 per cent of those with normal encephalograms responded favourably to the ketogenic diet. This method of study has since become almost essential in determining the type of treatment necessary.

A ketogenic diet, to be effective, must be rigidly controlled, and should be a weighed diet. It is necessary that in the diet the ratio of the ketogenic material to the anti-ketogenic be at least 3:1. This ratio is calculated according to Woodyatt's formula in the following manner:

$$\text{Ketogenic—90\% of Fat, 46\% of Protein}$$

$$\text{Antiketogenic—All of Carbohydrate, 58\% of Protein, 10\% of Fat}$$

$$\frac{\text{Ketogenic}}{\text{Antiketogenic}} \text{ or } \frac{\text{Fatty Acid}}{\text{Glucose}}$$

ratio is

$$\frac{.90F + .46P}{C + .1F + .58P}$$

We then calculate the diet for the individual patient as follows. For children the number of calories is 55 per kilogram, or 25 per pound of body weight. The amount of protein is set at 1 gram per kilogram body weight, which has been found quite satisfactory. The carbohydrate and the fat are then adjusted so that the ratio is as indicated and the calories are satisfactory for nutrition and growth. The caloric requirement is based upon the estimated weight for height, as given in standard tables.

It is seen that over a period of four days the carbohydrate in the diet decreases rapidly and

Boy, 8 years, 55 lbs. (25K)
Calories, 1375
(25 cals. per lb. body weight)
(55 cals. per kg. body weight)

	C g.	*P* g.	*F* g.	Cals.	*K* AK
1 day...	50	25	119	1371	1.5
2 day...	35	25	126	1374	2.0
3 day...	20	25	133	1377	2.7
4 day...	15	25	135	1375	3.1

the fat increases. This is advisable because most children placed immediately on the final diet will become nauseated and sometimes will have severe vomiting. However, with the plan indicated this very seldom occurs. In order to make certain that the patient is in ketosis a urine test for diacetic acid is done on the first morning specimen daily. This, the patient's mother can be taught to do quite readily. Patients must be kept on this diet, in ketosis, for a period of from six to twelve months. The carbohydrate in the diet is then gradually increased and the amount of fat reduced until the diet is essentially normal again; this usually takes place over a period of three to six months. The diet for an adult is the same in principle, although the caloric demand and the amount of protein necessary are different.

You are all, of course, familiar with the use of sedatives in epilepsy. The commonest drugs used are phenobarbital and bromides, or their combination. Some have advocated the use of phenobarbital with a ketogenic diet. A very useful combination to tide the patient over a disturbed period is sodium-phenobarbital in solution with various bromides. I should like to urge that when medication is given it be given in sufficient quantity, and that the patient be observed as frequently as possible. If these conditions are fulfilled, some patients will remain free from attacks for many years and perhaps permanently. Although phenobarbital is used so extensively, there is no satisfactory review of the results in epilepsy over a long period of years. It should be emphasized that in using diet or medication one must not lose sight of the necessity for healthy outdoor exercise or adequate rest and general hygienic measures. It is also a fact that constipation will increase the number of attacks. This should be guarded against by the use of mild saline cathartics and by dietary measures.

For many years surgeons have attempted to treat epilepsy by different forms of surgical procedures. With the increasing knowledge of neurosurgery these methods are becoming more rational and more effective, but are perhaps more often carried out in adults than in children. It is well known that a tumour may produce convulsive attacks, and many tumours may now be removed with very satisfactory results. Injury to the brain may produce a meningocerebral cicatrix, and this at a later date may give rise to epileptiform attacks. In some cases, this injury may have been so diffuse that the surgeon cannot hope to accomplish satisfactory results. However, in certain cases the lesion may be small enough to be completely removed. It is in these cases that the encephalogram may show us the location of the lesion. It must be remembered, however, that we must study the patient's history, the pattern of the seizures, the neurological examination, and finally the encephalogram, to determine what area of the brain has been involved. If these all point in the same direction, it is then considered advisable to explore the suspected area of the cerebral cortex with electrical stimulation. If the focus is found as suspected the area may often be removed with successful results. Penfield,[14] in the Montreal Neurological Institute, has within the last few years carried out a great many such exploratory operations. With his permission a summary of the results in his cases is given below. The majority of these cases are in adults but the problem is one which of course is not limited to children.

TABLE II.

CRANIOTOMIES FOR CHRONIC CONVULSIONS

	Number cases	*Per cent "cured"*	*Per cent improved*	*Per cent failures*
Excision of meningocerebral cicatrix..	22	46	32	23
Excision of focal cerebral cicatrix or focal atrophy....	22	41	32	27
Exploration without excision.....	24	8	12.5	79
Ligation of cerebral arteries.....	4	25	0	75
Evacuation of subdural fluid.....	3	33	33	33
Total craniotomies..	75	32		

(Operative deaths 2=2.6%).

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Case Reports

A CASE OF MASSIVE VOLVULUS OF THE SIGMOID WITH UNUSUAL GUT DISTENSION*

BY STUART W. LIPPINCOTT

Montreal

A volvulus is a common cause of obstruction. It is not confined to any single portion of the intestinal tract but may occur anywhere from the stomach to the sigmoid colon. The unusual feature of this case is not the situation of the volvulus but its enormous size without rupture or infarction.

The patient was 42 years old. He was confined to a hospital with dementia præcox for a number of years before the sudden onset of his fatal illness. Without warning he was suddenly seized with severe pain in the lower abdomen about 3 days before admission to hospital, became rapidly prostrated, ashen-coloured, cold and clammy. He began to vomit, but with no relation to the intake of food. His abdomen was distended and tender with no localized splinting. The temperature was 100° and pulse 88. The provisional diagnosis was intestinal obstruction. Morphia and enemas were given with no definite effect. The patient was transferred to the Royal Victoria Hospital, Montreal, in this condition. It was felt that in this moribund state surgical interference was not indicated. The abdomen rapidly became more distended and the patient succumbed within 5 hours. The final diagnosis was intestinal obstruction, probably due to volvulus.

A complete autopsy was performed 5 hours after death. External examination showed a body of large physique and moderate nutrition. The thorax was symmetrical, while the abdomen was markedly distended. On opening the thorax all the viscera were found in normal relation to each other. The lungs showed slight hypostatic congestion over the dependent parts and patchy emphysema of other portions. The other thoracic viscera showed nothing grossly abnormal.

The presenting abdominal situs was most unusual. Two tremendously dilated loops of large bowel were all that could be seen after slitting the peritoneum, which was smooth and glistening. These loops of bowel were deep red to purple in colour, but not gangrenous. They were parallel to one another in a diagonal position. The lower coil was the larger and appeared to be extending up from the pelvis, filling the right lower fossa and running across the abdomen to disappear under the left costal border. The upper smaller loop lay just below the right costal border and completely filled the costal angle (Fig. 1). It was impossible to recognize

Fig. 1.—Abdominal situs presenting two layers of markedly distended sigmoid colon.

definitely what portion of the bowel presented. On lifting up these loops they were found to be continuous and free above, forming an acute turn beneath the left costal border. The compressed cæcum and ascending colon were then readily defined. The greatly distended lower loop was attached to the posterior peritoneum at the pelvic brim and was thus identified as sigmoid colon.

There were two complete turns from right to left of the sigmoid on its mesenteric axis. The obstruction was produced by the cord-like lower descending colon and its mesentery tightly encircling the axis of the rotated bowel (Fig. 2). When the volvulus was un-

* From the Pathological Institute, McGill University, Montreal, Professor Horst Oertel, Director.

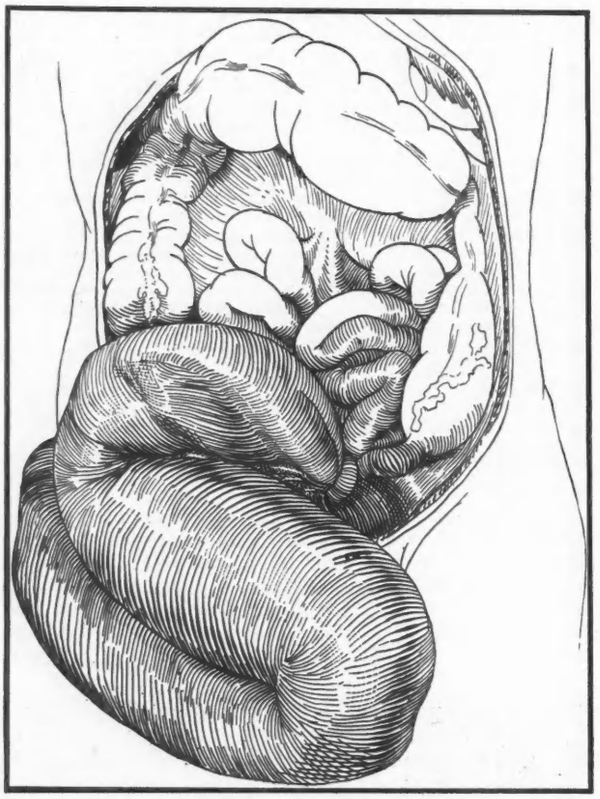

Fig. 2.—Reflection of loops shown in Fig. 1 demonstrating volvulus and small bowel pulled down into left lower quadrant.

twisted the upper smaller segment was found to be continuous with the descending colon, and the larger lower segment continuous with the collapsed rectum. The sigmoid mesentery had an extreme length of 25 cm. Its vessels were very engorged but contained only post-mortem clot. The entire length of the distended loop was 116 cm. and its greatest circumference 47 cm. These seem to be the largest measurements so far recorded. The proximal colon and small bowel were only slightly distended.

The wall of the distended sigmoid was obviously very thin and stretched, but still intact. Longitudinal streaking can be seen in the photograph. This is due to the separation and splitting of the outer smooth muscle striæ so that the definition of the three normal bands is lost in the larger loop. The mucosa was everywhere dark reddish-grey, thin, smooth, and intact. Turbid yellow fæcal fluid and gas filled the volvulus and entire gastro-intestinal tract to the rectum which was empty. The abdominal organs showed only passive congestion.

Histological sections confirmed the gross anatomical picture. The only noteworthy finding was the markedly thin, stretched coats of the sigmoid colon. The tissues throughout the different layers were compressed but remarkably well preserved. Terminal vascular districts were very engorged but there was no thrombosis or necrosis.

DISCUSSION

It has been pointed out repeatedly that the sigmoid colon is specially liable to become twisted because the base of its mesentery is comparatively narrow in proportion to its length. There is, moreover, a great normal variation in the length of this mesentery. Different investigators estimate the normal variation from 8 to 4 inches. It is argued, upon a mechanical basis, that the longer the loop and the nearer its two fixed ends are approximated, the greater is the liability to volvulus. We may perhaps assume therefore that a long mesentery and mobile sigmoid predisposed to the volvulus in this case. There is usually a long antecedent history of constipation. This can only be assumed in our case. The resultant dilated colon would be capable of greater acute dilatation without rupture or infarction than would be a normal sigmoid loop.

The inability of the colon to withstand extremely high pressure from within (even after death) has been demonstrated by Rotch, Fowler, and others. Rotch,[1] in studying a case of intussusception in a six months' old infant, made a ligature below the ileo-cæcal valve and found that a hydrostatic pressure of 180 cm. in height produced a transudate. Rupture did not occur until the pressure reached 268 cm. Fowler *et al.*[2] observed in the excised bowel of an adult with megacolon that the bowel with fæces weighed 3,900 g. The circumference was 47.5 cm. in the middle and the length 40 cm. The capacity, after fixation, was 2,250 c.c. Apparently the human colon can remain viable with a much greater degree of distension and lengthening than is generally appreciated.

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MYASTHENIA GRAVIS GREATLY BENEFITED BY INSULIN AS AN ADJUNCT TO PROSTIGMINE

BY J. L. ROBINSON

Toronto

Mrs. E.C., aged 63 years; weight 167 lbs., height 5 feet 9 inches. Her first symptoms occurred about two years ago as an inability to hold her eyes open, if at all fatigued; this lasted about a month.

On November 1, 1936, she had a fall downstairs, followed a week later by an acute arthritis in the knee, and this was followed by a generalized fatigue, more especially of the eye muscles, voice, neck, and left chest-wall. With that a failing appetite, sluggish digestion, insomnia, and loss of memory.

This phase was soon followed by a feeling of tingling and prickling all over on awakening, which would last for an hour or so, and then by a feeling of coldness and stiffness, especially of the upper arm

muscles, and quite frequently also in the abdominal muscles, which she described as a feeling of "plaster setting". Then came progressive loss of weight, strength and initiative; on the slightest exertion the weakness and fatigue of the eye muscles resulted in complete ptosis for half an hour at a time, accompanied by diplopia.

The patient was confined to bed from December 28, 1936, having lost 10 lbs. of weight in six weeks. Blood pressure, pulse rate, hæmoglobin, basal metabolic rate, blood count, urine analysis, electrocardiogram, all normal. The chest was screened and found normal. On March 11th the patient was put on glycine,[1] half oz., twice daily. On this she improved slightly, but the drug soon caused nausea, buccal and pharyngeal dryness, and had to be discontinued.

March 19th benzedrine sulphate, 10 mg., three times daily, was given without improvement in the local or general fatigue, severe attacks of which occurred several times daily for periods of 15 to 20 minutes, accompanied by pallor and cyanosis, and followed by distressing tingling all over, without sweating. After this she would be quite limp for an hour, and then would feel reasonably comfortable.

By the first week in April she became gravely ill, prostrated, appetite gone, sleeping badly, and with marked loss of weight, dehydration; she was fatigued with the slightest effort. Her eyes were very tired and heavy; she could not lift her arm from the bed. She had one almost total collapse, with cyanosis, dyspnœa, and rapid pulse, clammy sweats, loss of speech; this lasted about six hours. At this time it looked as though dissolution was imminent.

April 8th.—Two ampoules of prostigmin[2] 1.1 c.c. were given daily, with ephedrin, half a grain, orally after meals. The patient seemed to do well for two days; then she became more tired, more dehydrated, and emaciated more rapidly.

From April 18th to 25th she was at her worst. It was necessary to give prostigmin ampoules, four to six a day, to relieve the intolerable fatigue. Even under this treatment almost complete loss of appetite, extreme weakness, very marked dehydration, rapid emaciation, and mental apathy were noted. The patient complained of severe headaches and tremors to all parts of the body, having three to four spells of extreme exhaustion daily, each lasting about half to three quarters of an hour.

April 25th.—I considered that insulin might possibly be of some assistance, although the case appeared hopeless, and began with five units, three times daily, giving also three prostigmin tablets, and one ampoule of prostigmin, omitting the ephedrin. In two days' time, after beginning with insulin, the patient began to improve rapidly. By April 29th she was strong enough to be up for several hours at a time. By May 5th, the prostigmin ampoules were omitted.

The patient was then taken to the office for some short-wave treatments. These were given through the arms, knees, and head. She continued to improve rapidly, in weight, mentality, strength, appetite, and digestion. Within two weeks she had resumed her normal household duties.

By May 13th the insulin was decreased to five units twice a day, as she had regained her normal weight. From May 13th to July 12th she has been on insulin, five units twice daily, with prostigmin, one tablet three times daily. Her strength is splendid. She has resumed her full household activity; she goes to church, picture shows, and has stood a two hundred-mile motor drive in a day without undue fatigue. Occasionally the eyes tire slightly, and one arm feels a little heavy; twenty minutes short-wave treatment rapidly relieves these complaints.

It might be that the destructive action of choline esterase[3] on the acetylcholine at the myoneural junction[4] caused possibly a local carbohydrate starvation, and that insulin might augment the supply there. The clinical results have been so singularly satisfying up to date in this case that I feel my experience may be of benefit to others in this otherwise hopeless disease. One case is not enough to prove the contention, but its result invites a trial.

The prostigmine used was the product of Hoffmann La-Roche.

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EXPERIMENTAL STUDIES WITH SULFANILAMIDE AND WITH PRONTOSIL IN HÆMOLYTIC STREPTOCOCCUS INFECTIONS.—Mellon, Gross and Cooper report the results obtained by treating mice infected with hæmolytic streptococci of different virulence levels with sulfanilamide and with prontosil. Two strains of hæmolytic streptococci were used: the "Stoddard" strain, isolated from a case of septicæmia at the Western Pennsylvania Hospital, and the "Pion" strain, which was obtained from the Pasteur Institute. The former had spontaneously acquired high virulence without animal passage and was used at the time of maximal virulence and also during a period of spontaneously diminishing virulence. The latter culture was considered moderately virulent. Both sulfanilamide and prontosil exhibit marked therapeutic effects in mice against hæmolytic streptococcus infections. This effect obtains for strains of both medium and high virulence. Their experiments show no indication that phagocytosis is a factor in the mechanism of the therapeutic action of these drugs. Proper treatment of guinea-pigs with sulfanilamide results in a localization and rapid healing of experimental intradermal hæmolytic streptococcus infections, which in the untreated animals may disseminate with fatal results. No qualitative changes in the character of the histological response to the hæmolytic streptococcus as a result of sulfanilamide administration have been noted.—*J. Am. M. Ass.*, 1937, **108**.

Clinical and Laboratory Notes

"ST. LAWRENCE FEVER"

By H. E. MacDermot

Montreal

Those who have spent summers along the lower St. Lawrence are familiar with the well-recognized complaint in that region known as "St. Lawrence fever". I have observed this now for several years at points below Quebec (on the south shore) and I think there are aspects of it which are worthy of discussion. Many others must have had experiences similar to mine.

At all summer resorts there naturally will be minor complaints amongst those on holiday. Many of these can readily be accounted for by the sudden change from city life to the unusually energetic occupations that so many take up then, whether physically fit or not. Over-exercise and over-eating are common. In the case of St. Lawrence fever, however, these factors are not always present.

A typical case is as follows. Quite suddenly, usually overnight, the patient develops nausea, or vomiting, or diarrhœa with excessive gas and cramps, or a combination of these. The emesis is usually violent and continues until the stomach is cleared out. Occasionally streaks of blood are seen in the vomit, although no more than to suggest that the mucous membrane of the stomach must be engorged. The diarrhœa is sharp, but not prolonged. Fever is usually present, but not for more than a day or so. At times it is high and may be prolonged for as long as a week. This last, however, is rare in my experience. The pulse is not usually rapid. There may be some joint or muscle pains, headache, or even severe chills and sweating. Anorexia is complete. The respiratory tract is hardly ever involved.

If left alone, without any food at first except enough fluid to relieve thirst, the symptoms usually abate in two or three days. There are very seldom any complications, and there seems to be no special debilitation. If there is fever the recovery may be somewhat slower, but not necessarily so.

The treatment, as implied, should be complete abstention from food for about twelve hours, then sips of water or orange juice, and soft diet for the second day. Medication is impossible whilst nausea is present, but if there is only diarrhœa, a bismuth and opium mixture may be used to check it, if it is too severe. Castor oil I think an unnecessary torture in the presence of an already irritated, if not inflamed, bowel.

As already suggested, there is probably no single definite cause. The drinking water, the food, the climate, are all blamed in turn. The water supplies vary somewhat in different localities, but in such a village as Metis, with which I am most familiar, the water is above suspicion, and even before the present water-works were installed there never was any severe intestinal infection there. The food supplies present no peculiarity, unless it be from the point of view of the housewife, who finds the vegetable season to be somewhat later than inland. The milk is thoroughly well safeguarded. The climate is generally conceded to be extremely invigorating, but is subject to sudden and marked changes. A shift in the wind may produce a drop of 20 degrees in a few minutes. The sea bathing is cold.

When one considers the variety of circumstances in which these transient attacks occur, in both sexes, and at all ages, in natives as well as visitors to the locality, and in all kinds of weather, one feels that there is probably some special predisposing factor. There may be some vague climatic influence. It does not suggest an infection. At any rate, it is a malady in that part of Canada which one must be prepared to recognize as only a transient gastro-intestinal upset, even if sometimes distressingly acute. It is, on the other hand, just as important to remember that the onset of an acute appendicitis may exactly simulate St. Lawrence fever, before localizing signs appear.

Editorial

THE TOXICITY OF SULPHANILAMIDE AND ALLIED COMPOUNDS

WHEN any new drug of promise is introduced into the therapeutic armamentarium of the physician it is at first widely acclaimed and too widely exploited. It takes time for the enthusiasm to die down, but eventually, as observations multiply and are more critically analyzed, the true value of such drugs becomes manifest. These remarks apply with some force to sulphanilamide and its congeners. It is only some two or three years ago since this drug was introduced as an invaluable agent in the treatment of streptococcal infections, and already there is a mass of literature on the subject. Naturally, at first, clinical observations held the stage, but now we observe that the limitations of the drug are being discussed. The age, sex, and previous health of the patient; the location of the primary lesion, and the intensity of the infection; the dosage; the reaction of the patient; the fate of the drug when introduced into the body; all are attracting more attention. Very few studies on the toxicity of sulphanilamide are to be found at the moment, however; reference to the literature of the past two years reveals only a few, somewhat uncoordinated observations on the subject. Scientific investigation is just beginning. For much of the information given in this review we are indebted to the recent work of Perrin and Bliss[1] and of Hageman and Blake.[2]

In estimating the toxicity of any drug we have to take into consideration the amount administered and the period of time over which it is exhibited, in relation to the weight, age, sex and general physical state of the patient. The possibility of individual idiosyncrasy also should never be overlooked. What is a perfectly safe and justifiable dose for ordinary persons may be unsafe for some few individuals. In the case of new and poorly understood remedies special care should be exercised.

The first effect of sulphanilamide is on the stomach, and, as the drug is eliminated by the kidneys, on the urinary tract. Later, when the drug is thoroughly absorbed we get generalized effects, on the blood, nervous system, and skin.

Foules and Barr,[3] in 70 patients with proved puerperal sepsis, noted nausea and vomiting in one case after a total dosage of 75 g. spread over nine days; mild albuminuria (not present at first), was set up in two; and difficulty of micturition in three. Colebrook and Kenny,[4] and Frost[5] have recorded the onset of sulphæmoglobinæmia after the exhibition of prontosil (C. and K.), and after benzyl-sulphanilamide and prontosil (F.). The former observers, in 38 cases of puerperal infection treated with prontosil, had 3 cases of sulphæmoglobinæmia, one of which developed after the administration of as little as 4 g. of the drug. The authors quote van den Bergh and Revers, who think that the simultaneous administration of magnesium sulphate may have been a contributory factor in such cases. However, sulphæmoglobinæmia has occurred in cases where magnesium sulphate had not been used. Colebrook and Kenny think that the employment of saline cathartics in cases where prontosil is being exhibited may have something to do with the production of sulphæmoglobinæmia and advise against their use. Cyanosis, usually associated with methæmoglobinæmia, is a common manifestation. Jaundice has been reported in Montreal in one case.

Long and Bliss (*Canad. M. Ass. J.*, in this issue) state that in their experience prontosil

1. LONG, P. H. AND BLISS, E. A.: Para-amino-benzene-sulfonamide and its derivatives, *J. Am. M. Ass.*, 1937, **108**: 32; *ibid., Arch. Surg.*, 1937, **34**: 351; *ibid., Canad. M. Ass. J.*, 1937, **37**: (in press).
2. HAGEMAN, P. O. AND BLAKE, F. G.: Specific reaction to sulfanilamide: drug fever, *J. Am. M. Ass.*, 1937, **109**: 642.
3. FOULES, M. A. AND BARR, J. B.: Prontosil album in puerperal sepsis, *Brit. M. J.*, 1937, **1**: 445.
4. COLEBROOK, L. AND KENNY, M.: Treatment of human puerperal infections and experimental infections in mice with prontosil, *The Lancet*, 1936, **1**: 1279, and 1936, **2**: 1319.
5. FROST, L. D. B.: Sulphæmoglobinæmia following antistreptococcal chemotherapy (with benzyl-sulphanilamide and prontosil, sulphanilamide derivative), *The Lancet*, 1937, **1**: 510.

solution has produced but one effect—fever. They have not noticed renal irritation. They remark that in as much as sulphanilamide and its derivatives contain the benzene ring the drug may at times be found to damage the hæmatopoietic system. In fact, acute hæmolytic anæmia has been reported in a few cases.[6] Agranulocytosis has also been reported by several, notably, by Young.[7]

Massell,[8] in 14 patients treated with sulphanilamide reports 4 cases of drug rash, but his record is incomplete. The rash disappeared when the drug was discontinued and reappeared when it was resumed. One patient developed a leucopenia of 3,700. After discontinuance of the drug the white cells returned to their former normal level.

Hageman and Blake (*loc. cit.*) in 34 cases of various infections treated with sulphanilamide noted a characteristic febrile reaction (drug fever) in 21 cases. A rash, a maculopapular erythema in most cases, but sometimes urticarial and petechial, occurred in 9 cases. The authors remark upon the resemblance of the fever to serum sickness. Generally, the fever came on abruptly between the seventh and tenth day of treatment, and was usually attended by malaise, nausea, itching, and tinnitus. Precipitin, patch and intradermal tests, passive sensitation tests, and attempts to produce anaphylaxis and skin sensitivity, all were negative. Thus far attempts to throw light on the mechanism of this febrile reaction have failed.

Several authors have noted that the rash appeared only on those parts of the body which have been exposed to sunlight. The occurrence of fever in cases where prontosil is being exhibited, creates certain diagnostic difficulties, especially in the absence of a rash and where the fever of the disease is merged with that due to the drug.

Clinical acidosis has been observed in several instances. A rare complication, apparently of a toxic nature, is optic neuritis a case of which associated with the administration of sulphanilamide has recently been reported by Bucy.[9]

While this editorial was passing through the press some twenty deaths have been recorded from the use of a pharmaceutical preparation of sulphanilamide. At the moment it is not clear where the fault lies, and the investigation is difficult and likely to be lengthy. Possibly the sulphanilamide itself is to blame, or, again, the mixture in which it was exhibited was incompatible, or there may be other factors. It has been advanced that the poisonous effect was due to diethylene glycol in the carrying vehicle. A large proportion of the deaths occurred in children, and this suggests some revision of the dosage. It is clear, however, that the preparation of elixirs and other pharmaceuticals containing sulphanilamide must be carefully considered and supervised. Current issues of the *Journal of the American Medical Association* should be watched for developments.

Up to the present there is no evidence to show that the commoner toxic effects of sulphanilamide are specially serious or threatening to life, but we, nevertheless, should be on our guard. Possible cases of sulphanilamide intoxication should be thoroughly studied and carefully reported. We may then be able eventually to assess the situation properly. A.G.N.

6. KOHN, S. E.: Acute hæmolytic anæmia during treatment with sulfanilamide, *J. Am. M. Ass.*, 1937, **109**: 1005.
7. YOUNG, C. J.: Agranulocytosis and para-aminobenzene-sulphonamide, *Brit. M. J.*, 1937, **2**: 105.
8. MASSELL, B. F.: Studies on the use of prontolyn in rheumatic fever, *New Eng. J. Med.*, 1937, **216**: 487.
9. BUCY, P. C.: Toxic optic neuritis resulting from sulfanilamide, *J. Am. M. Ass.*, 1937, **109**: 1007.

ARTIFICIAL HUMIDIFICATION

WE are accustomed to hear, and to say, in the summer months, that "the heat would not be so bad if it wasn't for the humidity". It is doubtful, however, if the converse is equally well recognized, namely, that the extreme cold would not be so hard to endure if it was not for the lack of moisture produced by the heating of our houses. What we have in mind is the overheated, though not necessarily stuffy, room, in zero weather, when after the least movement over the carpeted floor one becomes an uncomfortably overcharged electric battery, when silk crackles as it is touched, furniture

dries and shrinks, and one feels "prickly all over". Is there any definite pathological effect on the body from such low humidities? In this, as in other aspects of atmospheric conditions, we recognize that there are extremely wide ranges of tolerance, which, incidentally, is why there never will be a standardized ideal for ventilation conditions. But it is likely, to say the least, that in many if not most people the breathing of air which in some buildings ranges between very low percentages of humidity for many weeks of the winter has a drying effect on the nasal mucous membranes. From this comes not only discomfort but a greater tendency to develop colds.

It is not easy, however, to prove that there is any great necessity for air conditioning, on physiological grounds. Psychologically, yes; and æsthetically also. But the hygienist tells us that most rooms in most houses under ordinary winter conditions contain enough oxygen and not too much CO_2, and that in heated rooms the humidity is very rarely so low as to have any appreciable effect. In a recent study of air-conditioning, Yaglou writes*: "Under ordinary indoor conditions during the heating season, variations of humidity are relatively unimportant as far as warmth and comfort are concerned, and from the standpoint of health there are no data to prove that artificial humidification is necessary . . . No one disputes the injurious effect of low humidities on household furniture, but the argument about health has little foundation in proved fact." He states that the ordinary variation in humidity during the coldest months is between 20 and 30 per cent, but we feel that in our part of the world considerably lower figures are often reached in overheated apartments. Artificial humidification, however, is expensive, and if we are to advise it from the standpoint of health we should have some more exact knowledge. We agree with Dr. Yaglou that "the tendency to dryness of the nose and throat under low humidities and its possible effect on respiratory disorder should be investigated". H.E.M.

* YAGLOU, C. S.: The physical and physiologic principles of air-conditioning, *J. Am. M. Ass.*, 1937, **108:** 1708.

Editorial Comments

The Late George Henry Simmons, M.D.

We regret to have to announce the death in Chicago, on September 2nd, of Dr. George H. Simmons, Editor-emeritus of the *Journal of the American Medical Association.*

Dr. George Henry Simmons was the son of George Simmons, and was born on January 2, 1852, at Moreton-in-Marsh, Gloucestershire, England. Emigrating to the United States in 1870, he entered the University of Nebraska and took his M.D. from the General Medical College and Rush Medical College, Chicago. He first practised in Lincoln, Nebraska, and was the founder of the *Western Medical Review.* His success with this journal led to his appointment in 1899 as Editor of the *Journal of the American Medical Association,* which he led to a high peak of prestige and influence. Under his direction the journal increased its circulation tenfold. A few months after his appointment as Editor he was made Secretary of the American Medical Association, and continued in the two positions until 1911, when he resigned the secretaryship and became Editor and General Manager.

Simmons stands out preeminently among the leaders of our profession. He came to the American Medical Association at a time when there was much to be done, and he gave invaluable leadership, for he had vision, resourcefulness and energy. He made his journal a doughty champion of the highest ideals in our profession. Medical science, medical education, medical ethics, all were the better for his inspiration. And while he wrought for the good of the medical profession he did not forget the welfare of the public whom our profession serves. One of the greatest achievements of the American Medical Association was the suppression of the inferior medical schools and diploma-mills which had been a reproach to the medical profession of the United States. Dr. Simmons resigned his editorship on June 9, 1924, and was tendered a testimonial dinner at which striking tributes were paid to him by Dr. Harvey Cushing, Dr. Frank Billings, Dr. W. J. Mayo, and Dr. William S. Thayer. He was also presented with his portrait, painted by Arvid Nyholm. After his retirement from active work Dr. Simmons lived in Florida, on the seacoast. He never lost his interest in things medical and was a great traveller until advanced age.

We may well see in the subsequent course of our great contemporary the spirit of its Editor-

emeritus, for the *Journal of the American Medical Association* has always stood for the best in medicine, and under its present editor, Dr. Morris Fishbein, has climbed from heights to heights, until now it is one of the most influential medical journals in the world.

A.G.N.

The Anatomical Society's Fiftieth Birthday

The Jubilee Meeting of the Anatomical Society of Great Britain and Ireland was held at Oxford in July, and marked the completion of fifty years of notable progress in anatomical teaching and research. Thirty-five papers were listed on topics showing a wide range of interest. At least nine were of embryological nature, and explained formative processes, such as the development of the supra-umbilical wall and the vagina. The influences of all growth-promoting and form-modifying hormones are included in modern anatomical science, and so we find titles like "The Effect of Sex Hormones on the Growth of the Seminal Vesicles". Subjects in the field of histology were numerous, and these studies were often carried out under various experimental conditions, as in that on the influence of enterectomy on the blood lymphocytes. Papers under such headings as "Vestibular Nuclei", "Thalamus", and "Anatomy of Taste" represented neuroanatomy. The older gross anatomy was illuminated by studies on the living, as in the kinema film showing movements of the joints. The prevailing trend towards functional interpretations is seen in such subjects as "Stress and Structure in Synovial Joints". The practical clinical bearing of the newer anatomy was evidenced in such captions as "Comparison of Percussion and Radiography in Locating the Borders of the Heart", and "The Effect of Posture on the Position of the Diaphragm". That anatomy, in its pursuit of wider interests, has not lost sight of surgical needs is proved by the inclusion of papers like that on "Replacement of Semilunar Cartilages after Excision". There were, too, goodly representations of comparative anatomy and physical anthropology.

Professor Barclay-Smith, the Secretary of the Society, had prepared a brochure in honour of the event, entitled "The First Fifty Years of the Anatomical Society of Great Britain and Ireland —a Retrospect", which afforded much interesting reading. The *facsimile* of the original roster of May 6, 1887, presents the signatures of twenty-eight Fellows and three visitors. Professor-emeritus R. W. Reid, to whom the book is inscribed, is the only surviving member. The list includes well known names like those of Arthur Thomson (who died recently, aged 77), G. D. Thane, J. Hughlings Jackson, and J. Bland Sutton. Short biographical notes are given of the original signatories whose interest in the Society persisted, and also of some of those who joined later, as Turner, Cunningham, Macalister, Cleland, Symington, Elliot-Smith, Gaskell, Moynihan and many others. There is a history of the Society's influential publication, the *Journal of Anatomy*, and a note on "Terminology" in which Prof. T. B. Johnston and his colleagues are given credit for their work in favour of an international anatomical nomenclature at the Milan International Anatomical Congress in 1936. The book has as its frontispiece a handsome portrait of C. B. Lockwood, the Society's founder, who was also its first Secretary and, later, a President.

May we congratulate the Society upon the attainment of its fiftieth birthday under such happy auspices, and may we wish for it a continuance throughout the next half-century of the vitality and usefulness which have marked its past record.

CHARLES C. MACKLIN

Birth Control in the United States

A recent decision of the United States Court of Appeals marks the end of a 60-year struggle to make clear that the federal obscenity laws do not apply to the legitimate activities of physicians. The original Comstock Act of 1873 was "for suppression of trade in and circulation of obscene literature and articles of immoral use", and contraceptive pessaries were held to come under the latter heading. The later interpretation of this Act, however, wisely recognizes that properly controlled contraception has become a part of preventive medicine, and that the earlier sweeping condemnation of the work and views of leading medical minds was not in the spirit of the Act. The decision was arrived at in a test case on the importation of some Japanese pessaries, sent to a physician for research purposes. The National Committee on Federal Legislation for Birth Control, whose President is Mrs. Margaret Sanger, deserves high praise for its resolute effort to establish such an important understanding.

H.E.M.

Special Article

THE CORRELATION OF THE PATHOLOGICAL AND SURGICAL*

BY J. K. McGREGOR AND W. J. DEADMAN

Hamilton, Ont.

The pathologist and surgeon necessarily have much in common. Both should be excellent clinicians. The surgeon should be able to make an accurate pre-operative diagnosis in the great majority of his cases. He must know signs and symptoms and have a clear idea of the underlying pathology. The resourceful surgeon will be able to recognize, in the gross, a high percentage of the pathological conditions which he finds at operation. He must be familiar with the various types of tissue reaction to insult, whether it be traumatic, inflammatory, degenerative or neoplastic. Recognition of the resu ts of trauma, of course, depends mainly on anatomical knowledge. Inflammatory lesions are most commonly due to bacterial action, and, while exact bacteriological knowledge is not absolutely necessary, and not practicable in many cases at the time of operation, yet the surgeon must be able to recognize the difference in tissue reactions to such things as *B. tuberculosis*, *Cl. Welchii*, and the pyogenic organisms. It is in the field of gross tumour diagnosis that his knowledge of pathology is most important. The diagnosis, at operation, of a lump in the breast is a case in point. If it be benign, simple excision alone is necessary. If it be of low-grade malignancy, breast amputation followed by irradiation may suffice. If it be markedly malignant, the somewhat crippling radical breast amputation is necessary. The decision as to which procedure will suffice is often crucial for the patient, and a prognosis is eagerly sought by the friends and family. A well trained surgeon should diagnose correctly, in the gross, about 80 per cent of his tumours; for the other 20 per cent, he needs the help of the pathologist.

The pathologist, in that he sees and studies all the tissue coming from the operating rooms of his hospital, naturally in the course of time becomes more familiar with the 20 per cent of difficult cases. Too, he has the advantage of the microscopic study of these difficult tumours. If his experience and ability are adequate, he should be able to correctly diagnose, in the gross, at least another 10 per cent, or 90 per cent of the total. Of the remaining 10 per cent he will have no difficulty with the aid of his microscope in diagnosing perhaps 7 per cent, and there will remain a small percentage which will puzzle even the best pathologists, and where it is advisable to secure several opinions. If there is much difference of opinion among good pathologists as to the benign or malignant character of any given tumour, it is more likely than not to be benign.

Both the surgeon who collaborates closely with the pathologist in the study of his tissue and the pathologist who collaborates closely with the surgeon in this work derive mutual advantage from it. The pathologist, in order to arrive at his diagnosis, makes a gross and microscopic study of the tissue, and derives great assistance if he is given the history and the clinical picture. The surgeon, to make his diagnosis, needs the history and clinical picture as well as the gross appearance of the affected tissue when he exposes it, and he derives great assistance from the opinion of the pathologist, based on the gross and microscopic study of the tissue removed. The patient is the chief beneficiary, and this, after all, is the important thing. The surgeon and the pathologist pool their knowledge and experience to this end in the surgical pathology laboratory, just as the physician and the pathologist do in the autopsy room.

Rapid tissue diagnosis by means of frozen section technique is one of the means to this end. This is particularly valuable as applied to the 10 per cent of tumours difficult of diagnosis in the gross. With a laboratory situated near the operating room, a section can be made and examined in four to five minutes, and with suitable tissues permanently stained frozen sections can be prepared in seven or eight minutes. By this means both surgeon and pathologist may get, as it were, a synoptic view of both gross and microscopic appearances. The advantages of rapid tissue diagnosis may be briefly stated as follows.

(1) *Accurate diagnosis* is possible while the patient is still on the operating table, so that the course and character of the operation may be modified to the needs of the case. (2) *Correlation of gross appearance and microscopic picture* is made possible at a time when both the operator and the laboratory man are concentrating on the case at hand, at which time the best impressions are recorded in the minds of each. (3) The *diagnostic ability* of both surgeon and pathologist is constantly improved. This is of particular advantage to the surgeon who operates at times where laboratory facilities are not available. (4) *The patient* gets the maximum service.

The disadvantages may be set down as follows. (1) *Not all tissues are suitable.* Minute pieces of tissue are much better handled by the paraffin method. Some specimens of uterine curettings are very unsuitable for frozen sections. (2) A small percentage of tissues require more

*Presented at the Annual Meeting, Ontario Medical Association, Toronto, May 30, 1934.

lengthy study, so that an impression given after a few minutes' glance at a rapidly prepared section may be valueless or at times misleading. This factor will depend, of course, on the experience of the pathologist and his degree of familiarity with the method.

The necessity for differentiating between chronic inflammatory change and the end-results of the normal involutionary processes in many of the organs subjected to surgical procedure calls for cooperation. The breast during pregnancy and lactation may sometimes show a hyperplasia of gland elements which simulates neoplastic change. The uterus during the menstrual cycle and after the menopause shows changes not at all associated with inflammatory processes. The thyroid shows varying grades of hyperplasia and involution which may be normal under the conditions in which it is functioning at the time. The appendix and ovary, as age advances, show a fibrosis and atrophy, the ovary showing cyst-formation, which is normal to it. All these changes must not be interpreted by the surgeon as well as by the pathologist as the results of chronic inflammatory processes, or as early neoplastic processes, to the end that unnecessary removal of organs be avoided. There has been too much surgery in the past, and it is a healthy sign that more conservative surgical methods are beginning to be adopted as a result of the knowledge gained by the closer association of surgical pathology with surgical practice.

There is, too, the question of the so-called pre-cancerous lesions. I know that the use of this term has the sanction of eminent authorities, and yet I feel that to make such a diagnosis is but begging the question. One may grant that chronic inflammation in glandular organs sometimes ends in malignancy, though this is not conceded by all authorities, and one may postulate that there must be at some stage a transition period, and, at the same time, disapprove of the use of the term in pathological diagnosis. It does more harm than good. Naturally, such a diagnosis leads the surgeon to adopt the same measures as he would if a frank diagnosis of malignancy were made. It seems to us that if a sufficiently thorough and careful microscopic examination of the tissue submitted be made an experienced pathologist should be able to give his opinion as to whether malignancy is or is not present, and should frankly give the surgeon the benefit of that opinion. He will make an occasional error, which must be allowed to even the best workers, but he will undoubtedly save many people from mutilating operations.

These problems arise in connection with many of the organs and tissues removed at operation, and it will be enough to discuss briefly a few of the more important. The question of pre-cancerous change in chronic inflammatory lesions of the breast comes at once to mind. The etiological relationship of chronic mastitis to mammary cancer is by no means proved. Bloodgood's study of a series of 350 cases of chronic mastitis, with ample follow-up, seems to point to the fact that cancer arises no more commonly in breasts the subject of chronic mastitis than would be expected, irrespective of the presence of this inflammatory process. If this is true, chronic mastitis with hyperplasia of gland epithelium or with intracystic papillomata is rarely, if ever, the forerunner of malignancy, and so the pre-cancerous condition does not ordinarily exist. In any case, as stated before, a frank statement of the presence or absence of malignant change in any given specimen is of much more service to the surgeon and patient, and is much to be preferred. The hyperplastic changes normally occurring in the breast during lactation or pregnancy can sometimes almost resemble neoplastic hyperplasia and should not be mistaken for it.

The female generative organs provide an exceptionally wide scope for surgery, and as one sees the procession of uteri, tubes and ovaries passing through any active surgical pathological laboratory, one can not help but wonder if removal is necessary in all cases. Endometritis is sometimes intractable, and a persistent metrorrhagia is bound to call for radical treatment, but at times the degree of disease to be found in the endometrium would not seem to warrant hysterectomy. Cervicitis is, no doubt, troublesome to treat and cure, but it does seem that extirpation of the uterus or even of the cervix is an admission of failure. Certainly, much advanced work should be undertaken in an attempt to get results by a less radical form of treatment. The development of involutionary change in this organ brings fibrosis, which may simulate, but is not associated with, chronic inflammatory change. Oöphorectomy is commonly performed for a cystic condition of one or both ovaries. It is to be remembered that cyst-formation is one of the functions of the normal ovary. Cysts will vary in size, but unless they have, or develop, some neoplastic properties they are usually self-limited, and unless large enough to completely eradicate normal ovarian tissue may not be pathological. Complete removal of such ovaries not only may not relieve the symptoms but will introduce the less desirable symptoms of the artificial menopause. A gradual fibrosis of the ovary progresses with the cyst-forming activity and is therefore a normal tissue reaction.

Various other organs present similar problems. As a vestigial organ, the appendix is subject to involutionary changes, and may, in later years, undergo a disuse atrophy. The end-results of these processes must not be confused with the end-result of a past chronic inflammatory process. The importance of distinguishing the two is seen when the question of prognosis enters, for removal of an organ not the seat of inflammatory change probably will not eradicate the symptoms distressing the patient. The carcinoid is the common tumour of the appendix,

and is usually benign, but the detection of the occasional one showing neoplastic change is a matter for surgical and pathological cooperation. Mesenteric lymph glands in the region of the appendix sometimes show enlargement in the absence of definite pathological change in the appendix. Study of a series of these failed to show *B. tuberculosis* as the etiological agent. The pathology of the lymph gland is one of the difficult fields, and the solution of many of the problems calls for the fullest co-operation. The distinction between miliary tubercles of the peritoneum and miliary metastatic carcinoma of the same organ can at times be made only with the microscope.

The surgical onslaught on the often inoffensive tonsil in children is happily lessening somewhat, it being recognized that, after all, only tonsils showing pathological lesions should be removed, and that in children the tonsils undoubtedly serve a very useful function until such time as they are so damaged as to not only lose this function but act as foci of infection. Tonsils, being lymphatic organs and the seat of much reticulo-endothelial tissue, probably have a great deal to do with antibody production in childhood, and should not be lightly sacrificed.

The thyroid gland introduces many perplexing problems. Normal processes of hyperplasia and involution ebb and flow in it, so that it is difficult at times to delimit the normal variations in structure. Excessive hyperplasia may produce nodules in the gland which are not in any sense adenomata. The question of the toxicity of adenomata needs further study. A large degenerating adenoma may not cause nearly as much toxicity as a smaller one with less degenerative change. The relationship of Riedel's "woody thyroiditis" to certain forms of carcinoma of the gland is not clear.

Perhaps the outstanding value to the surgeon of correlation lies in the fact that the pathologist is usually a salaried man who can and must be independent in thought, and who, to attain any prominence, must have built up a reputation for fearless honesty. His contact with the patient is not close. In fact he may sometimes be called upon to make momentous decisions without the patient being aware of his existence, and it is perhaps this factor which is responsible for the usual inadequacy of his stipend. However, he expresses an independent, honest opinion, and his errors should be in inverse proportion to his experience. His efforts should provide the surgeon with a factor whereby the latter may avoid having his opinions influenced by a desire to justify any honest mistakes he may make.

The ideal of the surgeon should be to interfere surgically only where necessary, and it is a notable fact that most surgeons become more conservative as their experience grows. The study of "living pathology" in the operating room, by both surgeon and pathologist, helps greatly to attain this end, and is perhaps one of the most important advances of the last generation.

Association Notes

The Canadian Medical Association—Alberta Division

The second annual meeting of the Canadian Medical Association—Alberta Division, which would have been the thirty-second annual meeting of the Alberta Medical Association had there been no amalgamation, was held at the Macdonald Hotel in Edmonton, on September 8, 9, and 10, 1937. The attendance was larger than for many years, which shows the active interest which our profession takes in the Association.

The various business and scientific sessions were ably presided over by Dr. W. Fulton Gillespie, of Edmonton. We welcomed to our midst the representatives from the Canadian Medical Association, Dr. T. Howell Leggett, the President, and Dr. T. C. Routley, the General Secretary, Dr. M. R. MacCharles and Dr. J. D. Adamson, both from the University of Manitoba. We extend our appreciation for the excellent addresses and lectures which they gave us.

Following the precedent of our national organization, no scientific papers were given the first day. Meetings were scheduled for the Board of Directors, the Board of Representatives, and the annual meeting of the College of Physicians and Surgeons, when the members of the Council gave an account of the work of the previous year.

In an address at a luncheon session, the President of the Canadian Medical Association outlined the responsibilities of our profession to the public. He remarked that "The science of medicine has advanced so rapidly, while medical economics has been almost standing still, that a serious disequilibrium has been created. One of the leading tasks falling the medical profession in Canada is correction of this unbalance." He urged the medical profession of Alberta to take the lead in formulating some plan whereby medical services will be available to all classes of people and at a cost within their means. In the belief that a practical scheme of aligning medical economics with progress in the practice of medicine the Canadian Medical Association had appointed a representative committee to study the problem of health services extension.

Dr. T. C. Routley stated that in Denmark, the state, in cooperation with the medical profession, has built the best public health service in the world, and one reason for their success

has been an ample supply of funds resulting from the health tax of 25 per cent of the tax dollar in that country. He described public health organizations in Great Britain, Denmark, Germany and France, citing observations made during a recent tour of these countries. In most European countries they have completed a framework on which, it is felt, will be constructed an advanced health service. In Canada it is our job in the medical profession to give leadership in all questions of public health.

Dr. J. S. McEachern, of Calgary, addressed a largely attended public meeting on the subject of cancer. He stated that preliminary steps in organization of a continent-wide campaign against the scourge of cancer were under way. The first major move in the direction of organized combat against cancer was made last February when the Canadian Society for the Control of Cancer was formed as an auxiliary to the King George V Silver Jubilee Cancer Fund for Canada. It is expected that there will be an organization of branches in every province in the Dominion.

The scientific papers presented at this year's meeting were of much practical value. A new feature introduced was short talks on therapy. It is to be hoped that this valuable addition to our program may be repeated next year. The following films, approved by the American College of Surgeons, were shown: Emergency care for safe transportation in fractures of long bones; the valves of the heart in action; cardiac irregularities; the treatment of burns; prevention and treatment of eclampsia; pernicious anæmia; intra-cranial injuries of the new born. Pathological, dermatological, radiological and orthopædic exhibits were presented by the University of Alberta.

At the installation of the new president of our Association, Dr. J. K. Mulloy, of Cardston, by Dr. Kerr, President of the University of Alberta, a gavel was presented. The wood from which this was made has a historic background, as part of the gavel is made from wood of the first orderly room of the Royal Northwest Mounted Police Barracks at Macleod, and from the chair made by Factor John Campbell, of Fort Chipewyan, and presented to Chief Factor John Rae more than three-quarters of a century ago.

The golf trophy presented by Dr. Alan Kennedy, of Macleod, in memory of his late father Dr. George A. Kennedy, who was one of the pioneer physicians of Alberta and a member of the first Council of the College of Physicians and Surgeons of Alberta, was won by Dr. Wallace S. Niewchas, of Edmonton.

The wives of the out-of-town physicians were entertained at afternoon tea by Mrs. Fulton Gillespie. Other forms of entertainment were provided for the guests.

The officers of the Canadian Medical Association—Alberta Division for 1937-38 are: *President,* Drs. J. K. Mulloy, Cardston; *President-elect,* C. R. Bunn, Red Deer; *Hon. Secretary-treasurer,* George R. Johnson, Calgary; *Librarian,* G. E. Learmonth, Calgary; *Representative on the Executive Committee of the Canadian Medical Association,* W. S. Galbraith, Lethbridge.

Representatives on the Council of the Canadian Medical Association: Drs. J. K. Mulloy, Cardston; G. R. Johnson, Calgary; C. R. Bunn, Red Deer; G. C. Gray, Edmonton; R. B. Francis, Calgary; A. E. Archer, Lamont; I. R. Bell, Edmonton; A. I. Danks, Calgary.

Editorial Board, Canadian Medical Association Journal, for Alberta: Drs. G. E. Learmonth, chairman; T. H. Whitelaw; R. B. Francis; J. S. Wright.

Chairmen of Standing Committees.—Cancer Committee: Dr. M. R. Bow, Edmonton. *Medical Education:* Dr. D. Locke, Lacombe. *Maternal Welfare:* Dr. J. R. Vant, Edmonton. *Pharmacy:* Dr. I. Bell, Edmonton. *Public Health:* Dr. A. C. McGugan, Ponoka. *Finance:* Dr. G. R. Johnson, Calgary.

G. E. LEARMONTH

Hospital Service Department Notes

The Educational Preparation of Hospital Administrators

The day when any person—nurse, doctor, clergyman or accountant—could lightly assume the rôle of hospital superintendent would seem to be fast drawing to a close. The position of administrator (this term is now coming into greater use as it seems to imply not only supervision but initiative and leadership) is such a complex one and the importance of having a properly qualified administrator is proving so essential that more emphasis than ever before is being laid upon the preparation of applicants for these positions. The educational program of the American College of Hospital Administrators, of which body many hospital superintendents and Superiors in both the United States and Canada are Fellows or Members, is tending to promote better preparatory and post-graduate training in this field.

At its recent annual convention in Cleveland model courses of preparation for the post of hospital administrator were outlined by the Rev. Alphonse M. Schwitalla, S.J., President of the Catholic Hospital Association of the United States and Canada, and Dean of the

All communications intended for the Department of Hospital Service of the Canadian Medical Association should be addressed to Dr. Harvey Agnew, 184 College Street, Toronto.

Medical School at St. Louis University. The reverend Dean does not propose any halfway measures. He feels (and as editor of a leading hospital journal, and as hospital association head, his experience is considerable) that the basic education should not be less than that required for the position of head master of a high school, and that the administrator of the future should have had an educational preparation usually demanded for the Master's degree or its equivalent. The collegiate preparation of the student should be definitely correlated with a view to his future field of specialization.

The Bachelor of Science curriculum leading to a degree in hospital administration should include (1) a general educational preparation, comprising courses in English, modern languages, preferably German (we would probably favour French in Canada), general philosophy, a science, preferably biology, and history; (2) a basic professional division comprising courses in accounting and finance, management and organization and statistics; (3) a professional division giving courses in sociology, socio-legal work and hospital administration.

Having completed the Bachelor's course, the student would be eligible for an internship in a hospital approved for a "hospital administration internship". Here he should get rotating experience in (*a*) general administration; (*b*) management with reference to services and personnel; (*c*) plant management; (*d*) medical and nursing staff administration; (*e*) intensified experience in at least two of the hospital's professional departments. Graduate study should then be continued for a Master's degree. This could be done in one of four fields: (*a*) administration and organization; (*b*) management; (*c*) finance administration; and (*d*) community relations.

A physician who already holds the M.D. degree should be required before appointment as a hospital administrator to complete certain basic professional courses outlined above, or to give evidence that he has completed them during his collegiate years; or that his knowledge of these various fields is sufficient. Accounting, financial administration, statistics, and management should be considered indispensable. After completing the extra year or two required for the above non-medical training, the young physician should be asked to serve one, and possibly two, years in an administrative internship at the completion of which he would determine whether or not he wishes to progress towards a Master's degree in hospital administration, the procedure for which would be as already outlined.

Nurses desiring to become administrators in the future should have the education now implied in a Bachelor of Science degree in nursing or nursing education. The modifications desired were outlined by Father Schwitalla. Or a nurse who has completed her three years of the basic professional curriculum in nursing might consider such as a minor towards the Bachelor of Science degree in hospital administration. The further studies, including another year in the Bachelor of Science course, the administrative internship, and the further graduate work, would be as outlined above.

The preparation, as here outlined, is very rigorous and would narrow down the field of aspirants considerably. In itself this might be desirable, for many individuals, nursing, lay and medical, now feel competent to direct the destinies of great institutions on very meagre qualifications. Perhaps, with the steadily rising level of scholarship in all fields of work, these standards may not seem so impracticable within a surprisingly short time. The University of Chicago has already established a course in hospital administration, and shorter courses for nurses and others are available in several Canadian and United States universities. Undoubtedly, more of our larger hospitals are emphasizing proper preparation in the selection of administrators, but it will be some time yet before all of the smaller hospitals get away from over-emphasis on local acquaintance or birth, salary expected, and such factors. One serious possibility inherent in the proposal outlined above is that it would tend to materially reduce the number of medical men going into hospital administration. Doctors usually do not become interested in administration until their period of internship; otherwise they would have taken a business rather than a medical course. If they then must take several further years of specialized study, the number willing to do so will be markedly reduced, in all probability. If, however, they must do so to compete with a rising generation of highly trained non-medical administrators, there would seem to be no other alternative.

Medical Societies

The Academy of Medicine, Toronto

The Academy of Medicine held its first regular meeting of the session in Osler Hall, 13 Queen's Park, on October 5th. The meeting took the form of a dinner over which Dr. Charles H. Hair, the new President, presided. The Hall was filled to capacity. The guests included His Honour the Lieutenant-Governor of Ontario, Col. the Hon. H. A. Bruce, M.D.; Sir Robert Falconer, K.C.M.G.; President Cody, of the University of Toronto; His Worship the Mayor, Wm. D. Robbins; the Dean of the Faculty of Medicine, Dr. W. E. Gallie; the President of the Canadian Medical Association, Dr. T. H.

Leggett; the President of the Hamilton Academy of Medicine, Dr. L. L. Playfair; and the President of the Academy of Dentistry, Dr. Harvey Reid.

Features of the evening were the presentation of a replica of the presidential badge to the immediate Past-president of the Academy, Dr. Henry C. Wales, and certificates of Honorary Fellowship in the Academy to Sir Robert Falconer and President Cody. The recipients replied briefly, acknowledging their appreciation of the honour bestowed upon them.

President Cody spoke of the recent appointment of Prof. William Boyd to the Chair of Pathology in the University of Toronto. Dr. Boyd has written several text-books widely used in medical faculties, both of Canada and the United States, and comes to Toronto from the University of Manitoba with a reputation as an outstanding teacher. Dr. Cody also announced the appointment, as Research Professor in Organic Chemistry, of Dr. Hermann Fischer who recently has come to this continent from the University of Basle, Switzerland. He is the son of Professor Emil Fischer, of the University of Berlin, a very famous chemist. Dr. Fischer brings with him to the Banting Institute his father's well known collection of chemicals.

President Cody stated further that the University at the present time was enlarging the Connaught Laboratories for further research work and that plans were out for an addition of another floor to the Banting Institute, which would be gone on with as soon as funds could be raised. He also stated that he hoped it would be possible soon to have a new building devoted to the study of organic chemistry. In referring to insulin, President Cody said that it had been stated that profits from the sale of insulin had gone to persons interested in its manufacture. This, he said, was not the case, but all profits accruing from its manufacture were used in research work.

Doctor Hair presented his inaugural address as President, his subject being "How medicine is influenced by economic conditions". He outlined the future course that medicine should take in research and prevention of disease. He also stressed the advisability of the unification of the boards of health in the different provinces, suggesting a Dominion Board of Health cooperating with the provincial boards of health in all problems such as emigration, control of communicable diseases, etc. This Dominion Board of Health should have connections with boards of health in other countries and a voice in the deliberations on health matters of the League of Nations.

S. J. NEWTON MAGWOOD,
Honorary Secretary.

University Notes

Dalhousie University

Newcomers to the full-time staff of the Medical School are three in number. These appointments have been made in the Departments of Pathology, Biochemistry and Physiology.

Dr. C. W. Taylor, M.B., Ch.B.(Birmingham), becomes the new Assistant Provincial Pathologist and Assistant Professor of Bacteriology. He succeeds Dr. G. McCurdy, who has gone to British Columbia as Provincial Pathologist. Before coming to Dalhousie University, Dr. Taylor had been doing post-graduate work under the direction of Professor G. Haswell Wilson.

Dr. R. D. H. Heard has joined the staff of the Biochemistry Department. He is a graduate in chemistry of the University of Toronto (1929). He obtained his M.A. degree in 1930, majoring in biochemistry with Professor Wasteneys. He was appointed an 1851 Exhibition Scholar and proceeded to Manchester to work with Professor H. S. Raper, obtaining his degree of Ph.D. in 1932 from the University of Manchester. From Manchester he proceeded to the Department of Biochemistry, Oxford University. After a year spent with Professor R. A. Peters he returned to Canada, where he continued his work in the Department of Biochemistry of the University of Toronto, from 1933-35. From 1935-37 he was on the staff of the Connaught Laboratories. His investigations have been concerned with the mechanism of the synthesis of adrenalin, the vitamin B complex, the bacterial decomposition of phosphoric esters, and most recently the steroid compounds occurring in the urine of pregnancy related with œstrin.

Miss Rhoda Grant, M.A., Ph.D.(McGill), has joined the staff of the Department of Physiology as Assistant Professor. Before coming to Dalhousie she worked under the direction of Professor C. N. H. Long, at the Royal Victoria Hospital, Montreal, taking her M.A. in Biochemistry and Ph.D. in Experimental Medicine. Following this she spent one year in Europe, working with Professor Otto Loewi in Gratz, and with Professor Lovatt Evans in London. Since then she has spent three years at the University of Toronto under Professor C. H. Best, and one year as demonstrator in Physiology at McGill University, under Professor John Tait.

N. B. DREYER

University of Manitoba

The 1937-38 session of the Faculty of Medicine of the University of Manitoba began on September 20th. Dr. John A. Gunn, Professor of Surgery and Honorary President of the Medical Students' Association, delivered the inaugural lecture in the presence of President

Sidney E. Smith, Dean A. T. Mathers, Mr. Paul Tisdale, President of the Students' Association, members of the Faculty and students.

Dr. Gunn spoke of the changing aspect of medicine and quoted the inaugural address of Dr. Kerr, the first Dean of the school, in 1883, in which he urged the students to get a thorough grounding of the fundamental sciences. Dean Mathers and Mr. Tisdale spoke briefly, welcoming the students.

The University of Western Ontario

The following appointments to the Faculty of Medicine are announced: Dr. Igor N. Asheshov, Associate Professor of Bacteriology; Dr. Samuel A. MacDonald, Instructor in the Department of Surgery, and Dr. G. Beaumont Sexton, Instructor in the Department of Medicine.

Dr. Asheshov, a Russian by birth, a British subject by naturalization, obtained the Diploma of Physician, with distinction (*Cum eximia laude*), from the Imperial University of Saratov in 1916. Afterward he joined the Central Bacteriological Laboratory of the Armed Forces of South Russia under Prof. V. A. Yourevitch. In November, 1919, he was requested by the British Military Mission in South Russia to prepare a "vaccine" and inoculate all the members of the mission against typhus. In March, 1920, he was evacuated by the British forces from Russia to Salonica, where he was employed as Bacteriologist-in-charge of the Bacteriological Laboratory of the British Salonica Hospital. In July, 1920, he went to Yugoslavia where he became Chief of the State Bacteriological Laboratory at Dubrovnik (Ragusa). During 1921 he worked on an outbreak of plague at the Bay of Catarro. In 1928 he was invited by the Indian Research Fund Association (under the Government of India) to organize and take charge of the Bacteriophage Inquiry at Patna (Bihar and Orissa) under a contract for three years which was extended to cover an additional three years. In 1935 he worked at the National Institute for Medical Research in London, and subsequently continued his investigations at the London School of Hygiene and Tropical Medicine. Dr. Asheshov is the author of many papers on the bacteriophage.

Dr. S. A. MacDonald, B.A.(McGill), M.B., Ch.B.(Edin.), served a rotary internship in the Montreal General Hospital in 1930-31. He held the appointments of Demonstrator in Pathology, McGill University, and Assistant in the Department of Pathology in the Royal Victoria Hospital, Montreal, in 1931-32, and was surgical intern under Professor Evarts Graham at the Barnes Hospital in St. Louis in 1932-33. He served as assistant in the Department of Surgery at the Yale University School of Medicine and Assistant Resident Surgeon in the New Haven Hospital during 1933-35. Latterly, he has been Instructor in Urological Surgery at Yale and Resident Urologist in the New Haven Hospital.

Dr. G. B. Sexton graduated from Queen's University in 1930, and served a rotary internship in the Millard Fillmore Hospital in Buffalo. For 18 months he was associated with Dr. Herbert H. Bauckus in the practice of dermatology, and studied in the Department of Dermatology and Syphilology in the University of Buffalo. In 1933, Dr. Sexton became associated with Dr. Howard Fox, of New York, and held appointments in the out-patient departments of the New York University and Bellevue hospitals. After serving three months in the Willard Parker Hospital for infectious diseases in New York, he began practice in Ottawa, where he was appointed dermatologist on the staffs of the Ottawa Civic and Grace hospitals, and acted as consultant in dermatology for the Department of Pensions and National Health.

Letters, Notes and Queries

Mycosis Fungoides

To the Editor:

With reference to your query about the treatment of mycosis fungoides in the *Canadian Medical Association Journal*, October, 1937, page 400, the subject is fairly well covered in most of the recent dermatological textbooks.

Roentgen therapy is the most useful single agency. I have followed the literature fairly closely, since the ultimate prognosis is at present practically hopeless. Good results have been reported from malarial or electrically induced pyrexia. The most recent thing that has come to my attention has been sodium silicate, in doses of 2 to 5 c.c. of a 1 per cent solution. Improvement is reported and its further trial recommended in the *Archives of Dermatology and Syphilology*, 1937, **35**: 544. I would recommend reference to this.

D. E. H. CLEVELAND.

Vancouver, B.C.,
October 7, 1937.

Trench's Remedies Limited

To the Editor:

I am enclosing a circular advertising some tablets of which I would like to know the composition. If you are unable to give me any information will you please pass this along to the American Medical Association.

Yours very truly,

J. F. C. ANDERSON.

Saskatoon, Sask.,
August 28, 1937.

REPLY.—According to the circular submitted, the preparation in question is called "Trench's Tonic Tablets". We are told "The nervous strain which arises from the rush of modern life often leaves you with lessened ability to work and play, or to get the best results from your daily activities. A definite need exists for a tonic that will help to keep the human system in a healthy condition, so that you may face the strain of a rapid, modern existence with confidence, and with full mental and physical powers." Again— "'Trench's Tonic Tablets' are specially prepared for the purpose of building up the system, giving renewed energy and a healthy appetite."

With this circular comes an order form for "Trench's Remedy", "Trench's Tonic Tablets" and "Trench's Stomach Tablets". The price ranges from $5.10 for a quarter package (six weeks' supply), $9.05 for a half package (three months' supply), and $16.60 for a full package (six months' supply).

We have referred this enquiry to the Bureau of Investigation of the American Medical Association, who have kindly replied as follows.

"We are enclosing a page from the pamphlet 'Epilepsy Cures and Treatments' containing a report on 'Trench's Preparation'. This information, as you will see, dates back to 1912, and whether the stuff is still one of the old bromide type of nostrums, we do not know. The modern 'epilepsy cure' exploiter, as you doubtless know, is pretty largely using phenobarbital in the place of bromides.

Very truly yours,
Bureau of Investigation,
FRANK J. CLANCY,
Director."

The report on "Trench's Preparation" runs as follows.

"Trench's Preparation. — This was earlier known as Trench's Remedy and was put out by Trench's Remedies, Ltd., Dublin, Ireland. It was advertised in the newspapers and booklets were sent out containing the usual testimonials. Part of the advertising puffery consisted of an alleged analytical report from a so-called analyst, one Granville H. Sharpe, of London. The Sharpe person made a business of furnishing certificates for pay. The nostrum has been put out in two forms—a liquid and a powder. It was sold in the liquid form in the British Isles and in the powdered form elsewhere. In both forms, the product was a bromide mixture. The liquid contained potassium bromide and ammonium bromide, with sugar and colouring matter; the powdered form was a mixture of brown sugar and potassium bromide, but contained no ammonium bromide. However, the amount of potassium bromide in it was greater than the combined ammonium and potassium bromides in the liquid.—*J. Am. M. Ass.*, June 29, 1912."

We therefore at the present time have no information as to the composition of the "Tonic Tablets". The preparations in question now hail from Toronto.—[EDITOR].

Abstracts from Current Literature

Medicine

Hypoglycæmia due to Insulin. Marble, A., *New Eng. J. Med.*, 1937, **217**: 130.

Causes of hypoglycæmia are: an overdose of insulin, too long an interval between insulin and food, too little absorption of food, or physical activity unusual to the individual.

Individuals vary in the level of blood sugar at which they experience hypoglycæmia and also in their sensitiveness to insulin. Patients with the severe juvenile type of diabetes are apt to be more sensitive to insulin than those in middle life with milder disease. Cachetic patients, such as those suffering from tuberculosis or cancer, may be extremely sensitive to insulin. They have low glycogen reserves. Symptoms of hypoglycæmia arise from lack of sugar in the fluid bathing the fixed tissue cells, especially those of the nervous system.

Reactions due to unmodified insulin commonly appear 3 or 4 hours after the insulin has been given; those produced by protamine zinc insulin are most likely to occur 12 to 24 hours after its administration. They are more apt to be night reactions. But night reactions are not so common now as with the former regimen.

A patient with a mild reaction is characterized by nervousness, trembling and sweating or faintness, hunger, weakness and fatigue. Paræsthesias affecting the mouth or tongue may be a sign. These symptoms may be attributed to stimulation of the autonomic nervous system. Since the introduction of protamine insulin headache, nausea and vomiting are seen. These symptoms may cause confusion in diagnosis between diabetic coma and insulin shock. Changes in the circulatory system include extrasystoles, bradycardia rather than tachycardia, increase in the circulatory rate.

Unconsciousness, unaccompanied by convulsions, is without apparent damage if the patient is kept warm. The chief danger lies in the possibility that the diagnosis of diabetic coma may be made and insulin given. This happened in the case of a 27-year old woman, who, on account of a diagnosis of diabetic coma instead of hypoglycæmia, was given 200 units of insulin. The mistake was discovered but she died without recovering consciousness in spite of a con-

stant administration of glucose that raised her blood sugar to normal.

It is hazardous for diabetics who are taking sizable doses of insulin to act as engineers, motormen, bus drivers, airplane pilots, switchmen in railway yards, crossing tenders, roofers, and so forth.

Only 32 fatal cases of hypoglycæmia have been reported in the literature up to 1932. Probably some of these died not from hypoglycæmia but from a complication. Since 1932 a few fatal cases have been reported. But it requires unusual conditions or poor treatment, or both, to cause a death from hypoglycæmia. Laboratory confirmation of the diagnosis is essential. If a patient cannot swallow, 20 c.c. of a sterile, buffered 50 per cent solution of glucose may be given intravenously. If this is not available a sterile 5 per cent solution may be given subcutaneously. If the reactions are due to protamine zinc insulin the patient may at times suffer a relapse of symptoms and repetition of medication may be required. Two cases of marked hypoglycæmia with true blood-glucose values of zero are reported.

LILLIAN A. CHASE

Adenoma of the Pancreas and Hyperinsulinism. White, V. W. and Gildea, E. F., *New Eng. J. Med.*, 1937, **217**: 307.

The effects of emotional factors, of changes in diet, and of the administration of acid or alkali on the symptoms of hypoglycæmia in a woman of 31 are described. The symptoms of hyperinsulinism were shown subsequently to be secondary to an islet-cell adenoma of the pancreas.

The patient was found to respond favourably to a high-carbohydrate low-fat diet, and to respond poorly to a low-carbohydrate regimen. The threshold for the development of symptoms was not appreciably affected by the administration of large amounts of alkali or acid. No direct relation between emotional tension and the onset of symptoms was definitely established. The adenoma was unusual in that it was calcified, and was found outside of the gland in the tissues surrounding the pancreas.

LILLIAN A. CHASE

Laurence-Moon-Biedl Syndrome. Cooperstock, M., *Am. J. Dis. Child.*, 1937, **54**: 334.

This syndrome, characterized by obesity, hypogenitalism, mental deficiency, polydactylism and pigmentary disturbance of the retina, is being observed more and more often as the medical profession becomes increasingly acquainted with it. The present family was of French-Canadian origin, with the father obese and a history of obesity in his family. Thirteen children were born to the parents, of whom eight were living. Two of those who died were premature twins. The fourth child, a girl, died at the age of 12. She had polydactyly, poor vision, and exhibited the obesity of the Fröhlich type. The status of her intelligence was not determined. The eighth child, a boy, died at the age of 13 months of pulmonary infection. He exhibited polydactyly and marked obesity. The twelfth child, a girl, died at the age of 3 days. She weighed 11 pounds at birth and had an extra finger.

Of the living children, 6 were normal, and the other 2 were the patients of the report. One, a boy, was seen at 11 years of age because of obesity and poor vision. His intelligence quotient was 66. When first seen there was a slight degree of hypogenitalism. There was a rudimentary nodule representing an extra finger on his right hand. The other child was the last in the family, a girl. She was 22 months of age, had just started to walk with support, but had not started to talk. She was markedly obese, with evidences of subnormal mental development, with one extra toe, and indication of an extra finger like that of her brother. She also had marked ptosis of the left lid. Thus 5 of 13 children had been affected in this family.

Reference is made to an article by Warkany, in which in addition to the five cardinal symptoms listed above, which were complete in only about one-quarter of the 102 cases reported in the literature, attention is called to other less obvious symptoms which may appear; nystagmus in 31 per cent of the cases; strabismus in 20 per cent; dwarfism in 17 per cent; deformities of the skull in 8 per cent; atrophy of the optic nerve without retinitis pigmentosa in 4 per cent; deafness in 4 per cent; congenital heart disease in 3 per cent.

MADGE THURLOW MACKLIN

Surgery

Torsion of the Fallopian Tubes in the Virgin. Blum, L. L. and Sayre, B. E., *Arch. Surg.*, 1937, **34**: 1032.

Torsion of the healthy Fallopian tube is of rather rare occurrence. The first operations for torsion of the normal adnexa in a virginal genital tract was reported by Stark in 1911, Norris, Cassidy and Northey in 1911, and since then by other surgeons.

The authors report the history of a girl, 10½ years of age, who was seized with severe right lower abdominal pain. Two days before hospitalization there had been no prior attack. The pain gradually subsided. She was nauseated but did not vomit. She appeared severely ill. Vaginal smears showed no evidence of gonococci. There was no evidence of *B. diphtheriæ* or hæmolytic streptococci in smears and cultures from the nose and throat. The leucocyte count was 18,200. Acute appendicitis was expected

and the child was operated on immediately. The appendix was infected and adhered to the omentum. A black, dark mass, the size of a large pea was found in the hollow of the sacrum, which proved to be the right Fallopian tube, which had twisted itself clockwise with three complete turns. The diagnosis was (1) massive hæmorrhagic infarction of the Fallopian tube with almost complete necrosis of the wall, and (2) chronic appendicitis.

The unusual features found in this patient were (1) the occurrence of isolated torsion of the Fallopian tube before puberty and the onset of menstruation; (2) a marked degree of hæmorrhagic infarction following torsion, and (3) association with periappendicitis. Various theories as to the etiology and mechanism of torsion of the undiseased Fallopian tube are presented.

G. E. LEARMONTH

Sclerosing Sarcoma of Bone. Lewis, D. and Geschickter, C. F., *Arch. Surg.*, 1937, **34**: 1010.

On microscopical examination sclerosing sarcoma of bone is found to be composed of large amounts of osseous and osteoid tissue which originate in the tumour. Clinically, a sarcoma of this type develops usually in the long bones. In the series of 158 cases reported by the authors 4 occurred in the skull, 10 in the upper and lower jaws, 3 in the vertebræ, 4 in the pelvic bones, and 4 in the scapulæ. It develops most frequently in adolescents and in young adults, and runs a rather acute course, the duration of symptoms rarely being more than six months. Pain, swelling and impairment of function appear in this sequence. Trauma was mentioned in connection with the tumour in approximately one-half of the patients. In children and young adults osteomyelitis may be simulated. The final diagnosis is based on the roentgenographical and microscopical pictures. The most common sites for development are the lower end of the femur and the upper end of the tibia.

In the authors' series it is noted that sclerosing osteogenic sarcoma is frequently not diagnosed in the early steps, due to two major factors; (1) there is a tendency to attribute symptoms to bursitis, neuritis, or such allied conditions and no roentgenograms are made; (2) roentgenograms are made but the early or sclerosing change in the end of the bone is either not seen or its diagnostic significance not recognized. The most characteristic location of the tumour is in the cancellous or cortical portions of the bone, though the prognosis is grave, but in this type of sarcoma permanent cures are noted more frequently than in other types of bone sarcoma. Radical surgical measures such as resection or an amputation were mentioned in all cases.

G. E. LEARMONTH

Obstetrics and Gynæcology

The Causes and Treatment of Retained Placenta. Currie, D., *Brit. M. J.*, 1937, **2**: 57.

Adherent placenta is much rarer than retained placenta. Adherent placenta occurs when the spongy layer of the decidua is absent and separation of the placenta is impossible. In retained placenta the placenta separates partially or completely but is not expelled from the upper segment of the uterus. The most frequent cause is uterine inertia. Other causes are placenta prævia, hydramnios, a full bladder, and fibroids.

Both Crédé's manœuvre and manual removal are dangerous methods to employ when the placenta is retained. Manual removal of the placenta is one of the most fatal of surgical procedures.

Injection of the placenta through the umbilical vein with sterile saline at blood heat is recommended as a safe and reliable method of effecting removal of a retained placenta. The umbilical cord is cleansed with spirit, the trocar and cannula are inserted into the umbilical vein about eight inches from the vulva, and held in place with a cord ligature; 450 c.c. of sterile saline at blood heat are then injected as rapidly as possible with a Higginson's syringe.

In the Leeds' records up to the end of the year 1935 the umbilical cord had been injected on 186 occasions. The death rate after this measure is employed is 1.6 per cent against 15.4 per cent after manual removal, and the mortality rate 8 per cent as opposed to 45.2 per cent.

Additional uses to which the injection of the umbilical vein can be put include prophylaxis against post-partum hæmorrhage, as a precaution in placenta prævia immediately after the delivery of the child, and as a means of clearing the field before suturing episiotomy wounds or tears accompanying difficult instrumental delivery.

ROSS MITCHELL

The Mechanism of the Prolongation of Pregnancy in the Rabbit. Koff, A. K. and David, M. E., *Am. J. Obst. & Gyn.*, 1937, **34**: 26.

The prolongation of gestation can be accomplished in two ways; first, by the induction of ovulation at the twenty-fifth day of pregnancy with the use of pregnancy urine extract, secondly, by daily intramuscular injections of progesterone, crystalline progestin, beginning as late as the twenty-eighth day of the gestation. In the first instance the new corpora lutea reach their maximum development and functional activity at term, thereby inhibiting the onset of labour and prolonging gestation until their influence has subsided, about fifteen days. In the second instance progesterone will likewise inhibit the onset of normal labour at term and prolong pregnancy as long as the injections are

maintained. Labour usually sets in twenty-four to forty-eight hours following the cessation of the administration of progesterone. The uterus is not responsive to huge doses of pituitary extract when under the influence of progestin. It appears that the maintenance of an adequate supply of corpus luteum hormone at term and beyond it definitely inhibits the onset of the birth mechanism.

When pregnancy is prolonged by new corpora lutea or by progesterone large post-mature fetuses are produced. If these are delivered before the thirty-sixth day of the gestation they are alive and normal. Intra-uterine death invariably occurs about this time, although the fetuses may be retained in the uterus as long as it is under corpus luteum influence. These experimental findings have their analogy to many pathological conditions in the human female.

ROSS MITCHELL

Ophthalmology

Anæsthesia by Sodium Evipan in Ocular Surgery. Nizetic, Z., *Anal. d'Ocul.*, 1937, **174**: 375.

The choice of anæsthetic does not always depend on the physician, but very often upon the patient who says he will have the operation only "if he is put to sleep first". This is usually true of operations on the globe. The author describes the use of evipan in a table of 115 cases showing sex, age, kind of operation, the amount used and results, and summarizes as follows.

Narcosis by sodium evipan is without doubt, as with other narcotics, a serious matter, but in his experience he has not had the slightest accident or serious complication, probably because he has kept the dosage moderate. The results in ocular surgery have been most satisfactory, where this form of anæsthesia has such particular advantages as allowing freedom of the operative field, improvement in asepsis security, and absence of pre- and post-operative inconveniences. Sodium evipan is a good drug, and may be used in urgent ocular surgery, in major operations, and the length of anæsthesia is quite sufficient for all ocular operations. In operation for detachment of the retina, Nizetic believes evipan to be the anæsthetic of choice.

S. HANFORD MCKEE

Ocular Pain. Its Treatment by Spheno-palatine Ganglion Anæsthesia and Orbital Alcoholization. Magitot, A., *Ann. d'Ocul.*, 1937, **174**: 361.

Ocular pain brings the patient to the ophthalmologist quite as frequently as visual disturbance. We will eliminate such causes as swelling of the lids, burns, and those caused by neighbouring sinus infection or dental abscess, and discuss only those related to the eyeball itself. Among these may be mentioned corneal erosions, which can usually be helped by the instillation of an analgesic.

Certain affections of the anterior segment of the eye, such as kerato-conjunctivitis, scleritis, parenchymatous keratitis, iritis, are usually accompanied by considerable pain, which is treated by certain drugs, the choice of which varies in individuals and by the local application of hot fomentations. We may also try a method which is without risk and which sometimes gives remarkable relief, that is sub-conjunctival injections of air. The technique is simple and consists in provoking a sub-conjunctival emphysema. Magitot has been using this method since 1912, and injects the air at four cardinal points, obtaining a large swelling about the cornea. The emphysema is usually resolved in about 24 hours but may remain a little longer. Sometimes these methods are insufficient, and it is necessary to use others. He suggests anæsthesia of the spheno-palatine ganglion and injections of alcohol in the orbit. These methods are described in detail and a commentary on the results is added.

S. HANFORD MCKEE

Urology

Retroperitoneal Perirenal Lipomata. Ockuly, E. A. and Douglass, F. M., *J. Urol.*, 1937, **37**: 619.

The normal fatty tissue which surrounds the kidneys may produce tumours that reach enormous size and produce death either through cachexia or by compression of vital structures. Perirenal lipoma must be differentiated from lipoma of the kidney which develops in the parenchyma at the expense of the kidney. A true perirenal lipoma must be a proliferative change in the normal fatty envelope of the kidney, lying in close anatomical relation to but not invading the organ.

Statistics show that by far the greater number occur in females, most frequently between the ages of 40 and 60 years, although a rare case is reported in the first decade. The onset is insidious and the tumours are usually painless. Symptoms of compression are also not frequent until at a terminal stage.

Urinary symptoms are usually conspicuous by their absence, and urinalysis reveals very little abnormal. The diagnosis is not always apparent, the symptoms are usually not suggestive, and examination is often misleading. The question of intra-abdominal, extra-peritoneal, intra- or extra-renal situation has usually been correctly answered by pyelography.

The treatment is operative in all cases; the transperitoneal route, usually employed. From

the fact that sarcomatous degeneration has been frequently observed post-operative irradiation is advisable. Two cases are cited. J. V. BERRY

The Effect of the Female Sex Hormone on the Male. Hamilton, J. B., Heslin, J. and Gilbert, J., *J. Urol.*, 1937, **37**: 725.

The authors have made careful studies of the influence of the female sex hormone upon the urological condition, blood chemistry, blood count, urine and basal metabolism of male patients who had received a series of injections of theelin in oil over a period of 26 days. Contrary to the claims reported in the literature, that there is an œstrogenic cause for prostatic growths, they observed that in men with a slight amount of residual urine, nocturia and other sequelæ induced by prostatic hypertophy (hence, sensitive indicators to any further growth of the prostate), no intensification of the symptoms occurred upon prolonged treatment with œstrogenic substances. Urethroscopic examination and histological sections of the prostate subsequent to the injections confirmed a lack of epithelial cornification or other growth.

The inhibition of the pituitary obtained with these dosages produced no striking relief of the symptoms accompanying benign hypertrophy of the prostate. Hence these facts do not support the theory that improvement in the condition of benign hypertrophy of the prostate may be obtained by inhibition of the pituitary.

J. V. BERRY

Neurology and Psychiatry

The Blood Calcium in "Idiopathic" Epilepsy. Munchin, H., *J. Neurol. & Psychopathol.*, 1937, **17**: 68.

In view of the suggestion that variations in the blood calcium might be a factor in some types of "idiopathic" epilepsy the writer presents the results of his personal studies together with a brief review of the literature.

In favour of the hypocalcæmic hypothesis is the increased frequency of convulsions during menstruation, when it is known that there are marked variations in the blood calcium. Other authorities have reported changes in the parathyroids, and one observer found beneficial results from the transplantation of parathyroid tissue into epileptics.

On the other hand the convulsions of beriberi and eclampsia have been conclusively shown to be unassociated with a low blood calcium. Numerous observers have reported normal figures, while Lennox and Allen are cited as finding in 77 cases normal blood values though the cerebrospinal fluid level was consistently low.

The writer then presents his personal studies of a group of 54 cases. Because of the suggestion that varying degrees of autonomic activity and altered blood sugar values may influence the level of calcium all specimens were taken under similar basic conditions. The values found were within normal limits, though the variations proved greater and the average a trifle higher than those reported for normal groups. To test out the suggestion of autonomic factors one group of patients was given atropine and another group, ephedrine. In neither was there any diminution in frequency of convulsions. The author concludes that the blood calcium of epileptics is normal. Neither alterations in blood sugar nor variable autonomic activity affect the blood calcium or the frequency of convulsions. G. PATERSON-SMYTH

Vascular Architecture of Lesions of Multiple Sclerosis. Putnam, T. J. and Adler, A., *Arch. Neurol. & Psych.*, 1937, **38**: 1.

It has long been known that there is a relationship between the location of the lesions of disseminated sclerosis and the veins of the nervous system. Small lesions usually surround small veins and the larger plaques form by coalescence. A similar relationship is found in cases of "post-infectious encephalomyelitis", while venous thrombosis invariably produces a lesion of the same general type as those seen in "encephalomyelitis" and disseminated sclerosis.

By means of ingenious glass plate reconstructions and other techniques the writers studied with meticulous care the vascular architecture of the plaque. They conclude that the pattern is characteristic. Small plaques tend to surround enlarged veins which are gnarled and tortuous. If a thrombus occurs in a vein an area of fresh degeneration appears in close relationship. In these sclerotic plaques there is usually an increase in number of capillaries, but a decrease may also occur.

G. PATERSON-SMYTH

Pathology and Experimental Medicine

Recent Findings in Solid Ovarian Tumours. Schiller, W., *Brit. J. Obst. & Gyn.*, 1936, **43**: 1135.

This chapter on ovarian tumours is especially written to convey to the gynæcologist what are benign and what are malignant tumours of the ovaries. This is necessary to eliminate disastrous results from extensive gynæcological operations where benign tumours are classified as malignant. The author traces their origin and shows how difficult a classification of ovarian tumours is because many differ greatly from the tissue of the gland in which they develop. The concepts of embryogenesis of the

ovary have changed our ideas, more emphasis being put upon the parent tissue and less on misplaced embryonal germs as formerly believed. Nowadays, we know that the germinal cells develop in the dorsal part of the primordial gut, and pass by way of the mesenterium to the gonad where the germinal cords, male and female, develop from the mesenchymal core of the gonad, and present in their development various phases in development of connective tissue or mesoderm. Cytologically, this tissue is determined even in its immature histological forms. Granulosa-cell tumours, arrhenoblastomata, dysgerminoma, and theca-cell tumours come under this category, and do not arise from follicle epithelium as previously described. Normal female parenchyma cells left as embryonic relics develop granulosa-cell tumours; normal male parenchyma cells left as embryonic relics develop into arrhenoblastomata; while neutrally determined parenchyma cells, left as embryonic relics develop dysgerminomata.

Granulosa-cell tumours develop from relics of the normal mesenchymal core of the ovary, never, as formerly believed, from the granulosa of the already mature follicle. The proliferation starts in the parenchyma, which first looks like a loose cellular fibroma. Later germinal cords develop. No ovula are present, therefore an irregular tumour network develops instead of parallel germinal cords. As the tumour matures more of the epithelial characteristics are revealed. The riper the granulosa-cell tumour becomes, the more it acquires hormonic function. The hyper-folliculin creates a hyperplasia of endometrium, resulting in metrorrhagia.

Arrhenoblastomata, arising from male types of embryonic cells, form germinal cords. They do not develop spermatogonia. As they mature these trabeculæ form lumen similar to that of male cords. Leydig cells, rich in lipoid, develop in the interstitial cells. A male hormone is secreted and produces masculinization features. These tumours are usually unilateral, benign, and look like granulosa-cell tumours macroscopically.

In dysgerminoma the mesenchymal cord of cells shows malformation in chromosomal development, is not determined sexually, and remains neutral. These tumours are composed of large, clear cells with vesiculated round nuclei and a narrow light protoplasm. Numerous lymphocytes lie in the connective-tissue septæ. Sometimes giant cells of Langhan's type are seen. These have lipoid in their protoplasm. Dysgerminomata occur in both women and men, and, if in the ovary, usually occur in the young, often before the thirteenth year, while in men they occur later in life. They are usually bilateral in women and have no hormonic influence. It is not necessary to follow operation by removal of the normal ovary or to radiate to produce sterilization.

Brenner's tumours, first described in 1907 by Brenner, were incorrectly called "oöphoroma folliculare". They arise from dislocation of gonad germs, therefore primarily belong to the urinary system. They are usually small growths from the size of a pea to chestnut and are placed near the hilus. They may be found in the walls of cystomata and dermoids. They have no hormonic value.

Xanthofibroma thecacellulare. These are like soft, cellular fibromas of the ovary, but are yellowish, and if soaked in Sudan become reddish because of lipoids in them. This fatty tissue stores hormones and gives rise to hyperplasias of the mucous membrane of the uterus, with resulting bleeding. They are embryologically related to the physiological theca. According to their nature in regard to storing folliculin or lutein tissue metrorrhagia or amenorrhœa results. P. J. KEARNS

Hygiene and Public Health

National Silicosis Conference. Summary Reports Submitted to the Secretary of Labour by Conferences Committees, Bull. No. 13, U. S. Dept. of Labour, Washington, D.C., Feb. 3, 1937.

In view of the many misunderstandings relative to the occupational disease silicosis, the U.S. Secretary of Labour on February 26, 1936, called together a group representing labour, capital, insurance, medicine, law, etc., to consider the matter. At this conference four committees were appointed to study the matters referred to them and to bring in reports at the next meeting of the Conference. These committees were as follows: (1) committee on the prevention of silicosis through medical control; (2) committee on the prevention of silicosis through engineering control; (3) committee on the economic, legal, and insurance phases of silicosis; (4) committee on the regulatory and administrative phases of silicosis.

These committees met in joint session on February 2, 1937, and the present report is a summary of the findings.

1. Committee on the prevention of silicosis through medical control. The report of this committee deals with such things as the definition and diagnosis of silicosis, percentage of free silica in different rocks, the relationship between silicosis and tuberculosis, the diagnosis and prognosis of silicosis, the estimation of disability, the incidence of disability. The committee points out that the hazard in different dusty occupations varies greatly and is dependent on many factors, most important of which probably are the percentage of silica dust and the size of the dust particles. In Barre, Vermont,

where the rock is 31 to 38 per cent silica, the maximum permissible concentration is set at 10 to 20 million particles per cu. ft. of air. In the gold mines of South Africa, however, where the percentage of silica is about 80 the maximum permissible concentration is set at only 4½ million particles per cu. ft. Suggestions are made as to prevention from a medical standpoint and regarding a medical educational program.

2. Committee on the prevention of silicosis through engineering control. This committee in its report deals with plant design and renovation, application of good housekeeping and maintenance to dust control, methods of ventilation and dust collection, wet methods, personal respiratory protective devices, determination of concentration and character of industrial dusts, employer and employee responsibility.

3. Committee on the economic, legal, and insurance phases of silicosis. It is estimated that about 500,000 workers in the United States are exposed to a serious silica hazard (1 per cent of the total employed population). Of these 500,000 probably about 110,000 have silicosis in some degree, of whom 4,000 to 5,000 are completely or partially disabled. To meet this problem the committee recommends legislation providing compensation to those who are disabled, and adequate legislation to insure proper preventive measures being taken where silicosis hazards exist. There is unanimity of opinion as to the desirability of enforcing preventive measures, but some disagreement as to the method of providing compensation for disability. The majority of the committee apparently favour some form of private or self-insurance, but some of the committee are strongly of the opinion that compensation should be provided through a state-operated fund. The great obstacle at the present time to including silicosis under workmen's compensation is the liability which has accrued over the years. Such a liability does not accrue in the case of accidents, but in chronic diseases the accrued liability is such that insurance companies have been known to refuse to carry the risk or to charge such high rates that employers are threatened with failure.

4. Committee on the regulatory and administrative phases of silicosis. This committee has considered the factors of compensation and prevention involved and the necessary organization of state units for preventing the disease through control of its cause. A number of principles are enunciated regarding the administration of compensation legislation. In regard to prevention the committee recommends that a bureau of inspection and a bureau of occupational hygiene should be created in each state. In the bureau of inspection there should be a sufficient number of inspectors to make at least annual inspection of all establishments having a silica dust hazard. The bureau of occupational hygiene should have sufficient personnel to handle with reasonable promptness both the specific problems which are brought to its attention by the bureau of inspection and also those problems which, of its own knowledge, constitute a potential or actual silicosis hazard.

FRANK G. PEDLEY

Obituaries

Dr. William John Malcolm Armstrong, of Mitchell, Ont., died on September 14, 1937, in his 80th year, after a lengthy illness. Previous to his illness he served as coroner and as M.O.H. Born on December 23, 1857, Dr. Armstrong attended the University of Toronto and after graduating (1889), he took post-graduate work in New York State. He practised for nine years at Fullarton Village before coming to Mitchell.

Dr. Olafur Bjornson, former Professor of Obstetrics in the Faculty of Medicine, University of Manitoba, died at the Winnipeg General Hospital on October 2nd in his 69th year. Born in Iceland, he came to Manitoba with his parents in 1876, in one of the great movements of Icelandic people to this country. He was educated in Winnipeg schools and graduated in Medicine in 1897. Five years later he did post-graduate work in Europe and Great Britain, particularly at the Rotunda Hospital, Dublin. Shortly after his return he was appointed to the honorary attending staff of the Winnipeg General Hospital, serving until 1932.

Possessed of those rare gifts, originality and humour, he contributed much to the college, hospital and community through his inspiring teaching, and he will be affectionately remembered.

Dr. Bernard Chiasson, of Eel Brook, N.S., aged 36, died recently.

Dr. Louis Napoleon Delorme, of Montreal, died on October 3, 1937, in his seventy-sixth year. Dr. Delorme was born at St. Jacques L'Achigan, Que. He completed his classical studies at the Joliette Seminary and took his medical course at the Medical School of Laval University (Montreal), now a part of the University of Montreal, from which he graduated in 1886. He had the extraordinary record of being Professor of Anatomy in the University for 49 years.

Lieutenant-Colonel John Nisbet Gunn, D.S.O., M.B., of Calgary, Alberta, died suddenly from a heart attack at his home on August 26, 1937. He was one of Calgary's leading citizens and prominent in many service and other organizations. He ranked high as a specialist in diseases of the eye, ear, nose and throat and during a period of over thirty years was recognized as one of the outstanding leaders on this branch of medicine in Western Canada.

Dr. Gunn was born in Beaverton, Ont., the son of Mr. and Mrs. Hector Gunn. He graduated in medicine from the University of Toronto in 1902. In the same year he went to London for post-graduate studies, and became a member of the Royal College of Surgeons and a Licentiate of the Royal College of Physicians. Returning to Canada in 1903, he became affiliated with his uncle, Dr. William Gunn, of Clinton, Ont., a well known surgeon, with whom he was associ-

ated for three years. In 1906 he went to Vienna where he studied for a period of nearly two years in diseases of the eye, ear, nose and the throat. He came to Calgary late in 1907, and almost from the time he began to practice he was recognized as one of high attainments in his special work.

Dr. Gunn had a distinguished record in the army. He joined the Canadian Army Medical Corps in 1909. He went overseas with the Canadian Expeditionary Force in 1915, with the rank of Major, and was later attached to No. 2 C.C.S. in France. In 1916 he was transferred to the 8th Field Ambulance, of which unit he became Lieutenant-Colonel, and held this position until March, 1918. On account of illness he returned to Canada in May, 1918. In the same year he was appointed D.A.D.M.S., M.D. 13. On the reorganization of the Canadian Militia in 1920, Lieutenant-Colonel Gunn commanded and raised the 8th Field Ambulance, perpetuating the 8th Field Ambulance C.E.F., commanded by him with much distinction during the war. He was mentioned in dispatches in 1917 and again in 1918, and was awarded the Distinguished Service Order. He was also granted the 1914-1915 Star, the British War Medal, the Victory Medal, and the Colonial Auxiliary Forces Officers' Decoration.

For more than twenty years Dr. Gunn was an active member of the St. John's Ambulance Association. He was commissioner for the Alberta Brigade during the past year. In recognition of his work he was made an officer of the Order of St. John of Jerusalem in 1935.

Dr. John Gunn was a man of many hobbies, in all of which he was keenly interested. He was fond of fishing, hunting, and dogs. He was one of the best dry-fly fishermen in Western Canada. In the motion pictures taken at Maligne Lake, Jasper Park, for the Federal Parks Department several years ago, he was the angler who was shown. He himself took many fine movie films of scenes in the Rockies. He was an expert shot, and was a charter member of the Calgary Gun Club. He was also interested in archery. His hunting dogs carried off prizes annually at the Alberta Field Dog Trials of which he was one of the provincial representatives. He was a charter member of the Calgary Archery Club; a member of the Alpine Club for more than 25 years; a Rotarian; a member of the Al Azhar Temple, A.A.O.N.M.S.; of Zetland Lodge, A.F.&A.M., Royal Arch Masons and Knights Templar. He took an active part in the activities of Grace Presbyterian Church and at one time served as president of the Men's Association of the Parish. Many hundreds of people of all ranks attended his funeral and many organizations were represented. He is survived by his widow, Anna; two daughters, Jeanette and Catherine; and a son, Ian. G.E.L.

Dr. George Crerar McIntyre, of Toronto, died on September 28, 1937. Dr. McIntyre was born in Paisley, Ont., and was in his fifty-third year. He attended Paisley schools and graduated in medicine from the University of Toronto (1915). Following the war he returned to Toronto and resumed his practice. For some years he served on the staff of the Toronto General Hospital, and was formerly on the teaching staff of the University of Toronto.

Dr. R. B. Pozer, of Ericksdale, Man., and his young son were killed in a head-on motor collision near Duluth, Minn., on August 28th. The doctor's wife and nephew were uninjured. Dr. Pozer graduated in 1923 from the Faculty of Medicine, University of Manitoba.

Dr. William Edward Rowley, of Saint John, N.B., died on October 8, 1937. He was born at Marysville, N.B., on June 25, 1876. Following public school, he attended Mount Allison University, Dalhousie University, and graduated in Medicine from McGill in 1896. His first practice was in Dalhousie, N.B. Dr. Rowley then became Superintendent of the old General Public Hospital in Saint John. Following this he studied for some time at the clinics in Austria and England, and on his return began practice in the city of Saint John. He was for many years an attending physician at the St. John General Hospital, and enjoyed an extremely large general and consulting practice. His opinion on chest, heart and gastrointestinal diseases was much sought and much valued. His was a most retentive memory which was stored with clinical experiences and curious facts. In the course of conversation these would be produced with a most telling effect. A good sense of humour, added to this excellent memory, made "Bill" Rowley a raconteur, famous in a province known for its story-tellers. He held a warm place in the hearts of his colleagues as a "good fellow" apart from his professional attainments. He was an expert angler and had fished most of the important trout and salmon streams in Eastern Canada. He was keenly interested in welfare work and had been president of the Saint John Family Welfare Association for some years.

Dr. Robert David Sanson, of Calgary, Alta., died on August 14, 1937, in his seventy-fourth year. He was born in Toronto, the son of Mr. and Mrs. Alexander Sanson. He was educated at Upper Canada College and at Trinity Medical College, where he received his M.D. degree in 1891. Following his graduation he attended Edinburgh University.

Dr. Sanson came to Calgary in 1892 and was the sole survivor of those physicians who began practice in this city in the early nineties. He held the position of Acting-Assistant Surgeon in the Royal Northwest Mounted Police for several years.

He enlisted in the Canadian Army Medical Corps in January, 1916, and went overseas in March of that year. He was injured in July, 1916, and in October returned to Calgary. He was appointed officer in charge of the Ogden Military Convalescent Hospital, which position he retained until he took charge of the Dominion Pensions Department for the Calgary District. He served in this position until 1934, when he was retired, having reached the age limit.

Dr. Sanson was one of Nature's finest gentlemen. In his younger years he was an ardent sportsman and a keen cricketer. His wife predeceased him by several years. He is survived by his daughter, Mrs. A. C. Newton, of Calgary.

Dr. Gerald Wilsdon Stanley, of Highgate, Ont., died on August 3, 1937. He was a son of Mr. and Mrs. James A. Stanley. Dr. Stanley was a native of Ballymote and a graduate of the medical school of the University of Western Ontario (1928). Then for a year he was on the medical school staff in London, Ont., and for a year on the staff of Harper Hospital, Detroit. He finally set up practice in Highgate.

Dr. Nelson Ford Sutton, of Norwood, Ont., died on August 21, 1937. He was a graduate of the University of Toronto (1903).

News Items

Great Britain

Lord Nuffield, Honorary Freeman of the Society of Apothecaries.—Lord Nuffield's great and generous services to medicine received further recognition recently when on August 17th the honorary freedom of the Society of Apothecaries was bestowed upon him at a full meeting of the Court of Assistants. Introducing to the Court "our distinguished visitor, whom you are about to admit to the honorary freedom of this ancient society of craftsmen," Dr. E. W. Ainley Walker said that Lord Nuffield was especially known to the medical profession by the splendour of his munificent benefactions to medicine and by the magnificence of his noble deeds. In every department of sound and sane humanitarian effort his name held a foremost place. The extent of his generous gifts and immense endowments was almost unprecedented. The greater part of these had been devoted to the alleviation of suffering and the improvement of the health and well-being of the less favoured of his fellow countrymen. The Master of the Society of Apothecaries, Dr. A. P. Gibbons, then presented to Lord Nuffield the certificate of freedom in a casket of cedar wood cased in royal blue morocco leather, bearing the Society's coat of arms in gold. The ceremony was followed by a Court dinner. It is customary at Court dinners that there should be no speeches, but on this special occasion the Master said he would break the custom. In proposing the toast "Our New Honorary Freeman", he said in a brief and gracious speech that Lord Nuffield had conferred enormous benefits on medicine and humanity in general, and had honoured them by accepting the freedom of the Society. In reply, Lord Nuffield said that he would like them to feel how deeply he appreciated the honour bestowed upon him. He would in the future try to continue to do what he had done in the past, and to help medicine and surgery and the teaching that brought about the results that were being achieved today. He would do what little he could to alleviate human suffering. Those who had the advantage of good health should help those who were less fortunate.—*Brit. M. J.*

The William Gibson Research Scholarship for Medical Women has been awarded by the Council of the Royal Society of Medicine to Dr. Nancy E. G. Richardson, of London. She proposes to carry out research on carbohydrate metabolism in pregnant and lactating women in relation to the principles secreted by the anterior lobe of the pituitary body.

Alberta

Recommendations were made by the Council of the College of Physicians and Surgeons of Alberta before the special legislative committee, to inquire into the necessity of revising the Workmen's Compensation Act for the establishment of a remedial clinic, both physical and mental, where disabled workmen might be re-educated to be better able to take an independent place in society. Other recommendations were: The appointment of an Accident Prevention Committee to investigate and devise means for the prevention of accidents; the establishment of a system of first-aid training in industries and industrial centres by the St. John Ambulance Association; the appointment of a travelling medical inspector who, with the physician in charge of the case, will review all hospital cases; an arrangement whereby seasonal workmen engaged in power farming or threshing may be allowed to come under the provisions of the Workmen's Compensation Act, and that all artificial limbs, dentures and associated articles be subject to replacement by the Workmen's Compensation Board, if destroyed or damaged through accident; that all diseases such as rheumatism, neuritis, lung ailments, smoke poisoning, and others, which are directly traceable to or have arisen out of or in the course of employment of the workman be considered as disabilities under the Act and that compensation therefore be paid.

G. E. LEARMONTH

British Columbia

Several radiologists from British Columbia attended the Fifth International Congress of Radiology held in Chicago in September. Among them were Drs. F. H. Bonnell, Bede Harrison, C. W. Prowd, of Vancouver; Dr. B. R. Mooney, of Victoria, and Dr. Ethlyn Trapp, of New Westminster. Dr. Mooney has recently been appointed radiologist of St. Joseph's Hospital in Victoria and on the occasion of his introduction to the Board of Governors gave a verbal report of the proceedings of the Congress, which he had just attended.

The Revelstoke Hospital Society is considering a hospitalization plan for heads of families and their dependents under 21 years of age.

Similar hospital contract schemes are in operation in numerous small cities and towns of British Columbia and have been found very effective. They assure patients of the best treatment and attention at a minimum of cost, and assure the hospital concerned the payment for services rendered.

A special committee has been set up in the Vancouver City Council to consider the possibility of permitting sale in Vancouver of milk pasteurized in outside municipalities. The present by-law requires that pasteurized milk sold in the city be pasteurized within the city where it is subject to inspection by civic authorities.

Dr. J. W. McIntosh, Medical Officer of Health, Vancouver, has reported to the city council that consumption of codeine in British Columbia has dropped 80 per cent in two years. British Columbia's proportion of codeine sold in Canada was reduced from 22 to 6 per cent in the same period.

The British Columbia Optometric Association has been insisting for some time past that it be recognized by the Vancouver City Council in connection with optical prescriptions for relief recipients. It has been explained to their representative that prescriptions for glasses for relief cases are issued only by doctors, but the optometrists demand that their prescriptions also be paid for, as the doctors' are, from city relief funds. Doctors treating relief patients in their private offices are obliged at present to have their accounts reviewed by a medical committee appointed from the Vancouver Medical Association, but, as pointed out by the Social Service Administrator of Vancouver, if the optometrists' demands were met the latter would refuse to allow medical men to pass on their prescriptions. A committee of the council is at present investigating the question.

Up to September 30th only 3 poliomyelitis cases had been reported in Vancouver, one of which is in an adult. None of the cases are of serious character. The authorities of the Metropolitan Health Board are nevertheless adopting all precautions available for checking the development of an epidemic. A call has been issued to all persons who have suffered from poliomyelitis to donate blood for obtaining a supply of paralysis serum.

It is announced by the Vancouver General Hospital that a Drinker-Collins respirator has been pre-

sented to the hospital by an anonymous donor living in Vancouver. This has been ordered and will be ready for use early in October. D. E. H. CLEVELAND

Manitoba

Perusal of the report of the Health Department of the city of Winnipeg for 1936 leaves the impression that the city is remarkably well looked after under the capable administration of Dr. A. J. Douglas. The corrected combined infant death rate and stillbirth rate for 1936 was 66.3 per 1,000 total births, which is a record low in the city and one which compares very favourably with the lowest rate on the continent. Over 91 per cent of the 2,714 live births to Winnipeg mothers occurred in hospitals or maternity homes.

Seventy-eight per cent of the 18,000 gallons of milk consumed daily in Winnipeg is pasteurized, and 22 per cent raw but tuberculin-tested. Five cases of undulant fever were reported, but only 1 case of typhoid fever, with no death. One hundred and twenty-three cases of diphtheria were reported, with 6 deaths. While this is a considerable decrease over previous years, Dr. Douglas feels that sufficient advantage is not being taken of the value of prevention by means of toxoid.

The report calls attention to adequate housing. During the past five years only 1 house or suite has been provided for every ten marriages. The shortage of housing accommodation occurs particularly among low-wage earners.

Dr. E. S. Moorhead addressed the members of the Winnipeg Medical Society at the opening meeting on October 15th on "Group hospitalization", a subject which is attracting considerable attention.

ROSS MITCHELL

New Brunswick

At the meeting of the Union of Municipalities of New Brunswick there was much discussion *re* the cost of hospitalization of tuberculous patients, and in the discussion it was suggested that the Provincial Government should assume a greater share in this cost. It was also pointed out that in the opinion of the members of the Union there was need for another sanitarium in the northern portion of the province. The town of Grand Falls offered to provide a free site if the government saw fit to erect such a new hospital.

Cases of infantile paralysis continue to be recognized in the province, the larger number in the city and county of Saint John. At the moment about 129 cases have been positively diagnosed; the number of deaths is considered relatively small, and the number of cases of paralysis is as yet uncertain. The schools of the province remain closed, and in a recent broadcast, Dr. Wm. Warwick, Chief Medical Officer for the province, urged the parents to continue their assistance to the authorities by preventing the congregation of any large number of children.

Somewhat overshadowed by the epidemic of poliomyelitis, a large number of cases have occurred throughout the province roughly classed as cholera or dysentery. Among these, a number of cases of typhoid were isolated and a lesser number of cases of dysentery with characteristic bacteriological findings.

Hon. Dr. Wm. F. Roberts, Minister of Health of New Brunswick, has resumed practice, considerably improved in health.

Dr. G. A. Mowatt, of Campbellton, has been seriously ill following an operation. His condition at this writing is grave.

Dr. W. O. McDonald, of Saint John, has just returned from Boston, where he has been doing some further work in anæmia.

Dr. A. S. Chesley, of Saint John, has completely recovered following a cholecystectomy.

Dr. W. M. Jenkins, of Gagetown, N.B., M.L.A. for Queen's County, suffered a serious loss on October 8th, when a disastrous fire completely destroyed his well known house and fine farm buildings. The doctor's wife had a narrow escape from the fire, which broke out during the night. A. STANLEY KIRKLAND

Nova Scotia

The reported cases of infantile paralysis in the province since July 1st reached the total of 49. There were 3 deaths. At present the epidemic seems to be lessening.

The proposed new hospital for infectious diseases, to be erected near Rockhead Prison to replace the Quarantine Station at Lawlor's Island in Halifax harbour, will be erected soon. The Lawlor's Island Station was not considered adequate and convenient enough. Plans for the construction of the hospital have been completed and accounts for the building have been passed at Ottawa.

Dr. Charles Beckwith, since 1927 Assistant Medical Superintendent of the Nova Scotia Sanatorium at Kentville, has gone to Cape Breton, where he will be Divisional Medical Officer of the Provincial Department of Health. During the past year he has been engaged in post-graduate work in Toronto.

Dr. O. R. Stone, of Bridgetown, and Dr. R. H. Fraser, of New Waterford, have gone abroad to engage in further study. The former hopes to divide his stay between London and Edinburgh.

Dr. Norman Bethune, recently returned from Spain, spent a few days in Halifax where he delivered a public lecture in the Dalhousie University Gymnasium on medical work in Spain. He also visited local hospitals in the city. N. B. DREYER

Ontario

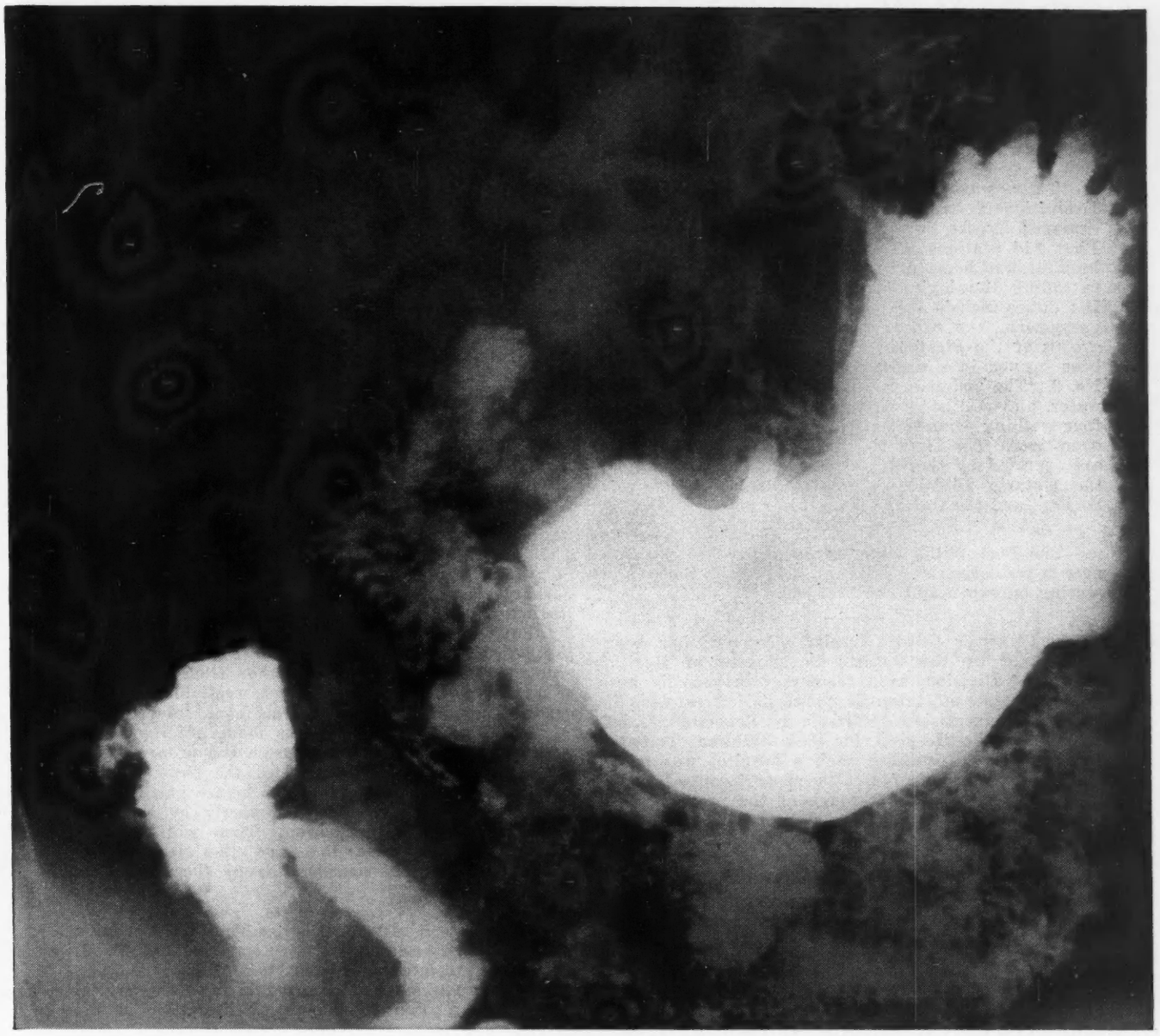
The Hamilton Health Association has received from the provincial government a cheque for $100,000. This money will be spent in building an addition of 21 beds to the nurses' home, a new 64-bed dormitory for male help, and centralization of the kitchen in order to improve the food service.

The Canadian Hospital Council, at its closing session in Ottawa on September 9th, elected as President for the next two years Rev. Geo. Verreault, of Ottawa University. Dr. Geo. F. Stephens, of Winnipeg, was elected Vice-president and Dr. H. Harvey Agnew, of Toronto, Secretary-treasurer. Dr. A. F. Anderson, of Edmonton, and Dr. A. K. Haywood, of Vancouver, were elected to the Executive.

There is considerable building activity in the Ontario Hospitals. Operations in the new Porcupine General Hospital were commenced last month.

On September 29th Dr. B. T. McGhie, Deputy Minister of Health, officiated at the turning of the first sod of the government hospital at Brampton. This hospital is intended for the treatment of tuberculous mental patients of the Ontario hospitals.

At Parry Sound a contract has been let for the erection of an addition to St. Joseph's Hospital at a cost of about $30,000.



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RADIOGRAPHS PROVIDE DIAGNOSTIC FACTS

The Peel Memorial Hospital at Brampton has undergone considerable structural changes. It is now a 60-bed hospital with modern operating facilities.

The Strathroy General Hospital is erecting a $3,500 staff residence.

There was exhibited at the Canadian National Exhibition a travelling hospital which had been equipped by the Superintendent of Ontario Highway First Aid Stations. This ambulance serves as office, hospital, and home for the Superintendent when he is patrolling the highway from Montreal to Windsor. His duties include the training of farmers, clergymen, garagemen, and other volunteers, to act as first-aid groups at the First Aid Stations which have already been opened in a number of villages along Highway No. 2. The ambulance is equipped with hot and cold water, and will accommodate two stretcher cases and four walking wounded. It is also equipped for minor operations. The First Aid Stations and the ambulance are operated by the St. John Ambulance Association, the Ontario Division of the Canadian Red Cross Society, and the Ontario Motor League.

The Fort William Sanatorium, with 103 patients now in residence, is to have an 80-bed addition, representing an expenditure of $125,000.

The former Grace Hospital, Toronto, has been taken over by the Ontario Department of Health, Hospitals' Division, as a temporary orthopædic hospital for cases of infantile paralysis. Treatment is under the supervision of Dr. D. E. Robertson, Chief Surgeon at the Hospital for Sick Children, Toronto. The decision to establish such a hospital was made by the Department of Health when it was learned that some 500 children throughout the province will require special orthopædic care as a result of poliomyelitis.

The Brantford General Hospital has received from the estate of Dr. James L. Gibson (Queen's '92), who died at Lynden, Ont., on June 10, 1937, an endowment or trust fund amounting to $2,000 and, in addition thereto, interest on the residue of the estate, to be used in rendering assistance to indigent patients. The Prince Edward County Hospital received a similar bequest from this estate.

Dr. G. Harvey Agnew, Secretary of the Department of Hospital Service of the Canadian Medical Association, was chosen President-elect of the American Hospital Association at its thirty-ninth annual convention in Atlantic City in September.

The completion of fifty years of medical practice by Dr. T. S. Philip, of Picton, was marked by a banquet given in his honour by the Hastings and Prince Edward County Medical Society, 60 medical men being present. During the evening Dr. Philip was presented with a gold-headed cane as a mark of the high esteem in which he is held by his fellow practitioners.

The old administration wing of St. Michael's Hospital, Toronto, has been replaced by a new one, which now completes the Bond Street frontage of the Hospital. On September 8th the new wing was opened by the Hon. Dr. H. A. Bruce, Lieutenant-Governor of Ontario, in the presence of a large assembly of guests, including Archbishop J. C. McGuigan, Sir William Mulock, Dr. H. J. Cody, and Senator F. P. O'Connor. The accommodation is now about 800 beds.

J. H. ELLIOTT

Saskatchewan

A plan has been evolved after discussion between the Government and a Committee of the Council of the College of Physicians and Surgeons, concerning the provision of adequate medical care to those in the drouth area. The following is a summary.

The grants to physicians practising in the rural drouth areas will be materially increased and mileage will be dealt with separately. A more detailed report will be completed than has been the practice formerly, and this will be reviewed by a committee of three physicians, which has already been nominated by the College and appointed by the Government. There will be grants to physicians in the smaller hospital centres to cover the care of relief patients referred from outside rural points, and also for mileage costs incurred in attendance on patients in the surrounding districts. The reports submitted will be reviewed by the committee. Physicians practising in urban centres outside the drouth area will be eligible for grants with reference to patients referred to them from the drouth area. The grant will be given on the basis of work done.

This plan is considered an emergency one, and will be in effect for the twelve months starting September 1, 1937. It was submitted to the Annual Convention of the College of Physicians and Surgeons and the Saskatchewan Medical Association, recently held in Regina, and was approved without dissent.

Payments made under this plan do not prejudice the position of the physician to collect his proper account for any work done, either from individuals or municipal units, when money is available, with the definite exception of physicians on municipal contracts.

All physicians and surgeons doing referred relief work must have authorization from the proper official of the municipal unit from which the patient comes, before his account for services can be recognized. The patient must also be referred properly by the local physician to the other physician. There will be exceptions in emergency cases; these and other circumstances will always be given consideration by the supervising committee.

The Prince Albert and District Medical Association held a dinner meeting in September. Dr. M. I. Humphries presented a paper on "Embolism", discussing the cases which had occurred in his own surgical practice in relation to the recent literature on the subject.

Dr. B. H. Lyons, of Birch Hills, spoke on "The treatment of sciatica", discussing the technique of injection and the results secured in a number of cases. Dr. D. P. Miller, member of the council of the College from the district, gave a report on the business section of the recent Provincial Convention in Regina.

LILLIAN A. CHASE

General

The College of Physicians of Philadelphia announces a series of scientific lectures to be given from October 6, 1937 to May 4, 1938. The speakers are Drs. H. C. Sherman, C.-E. A. Winslow, C. Macfie Campbell, Edward D. Churchill, D. W. Bronk, Harry Goldblatt, Warfield T. Longcope, Charles H. Best, and Russell M. Wilder. Dr. Best, of Toronto, delivers the Nathan Lewis Hatfield Lecture, his subject being "Recent experimental work on liver function".

International Conference on Hepatic Insufficiency.—Mr. Rucart, French Minister of Public Health, came to Vichy to open the International Conference on Hepatic Insufficiency which was held in that city on September 16th to 18th. This congress which counted more than 2,000 delegates from 43 nations was presided over by Professor Loeper, of Paris. Twenty-

five reports were discussed by renowned professors and doctors from the University of Vienna and some of the schools of London. During the morning the Minister of Public Health visited the famed Vichy springs and the new installations of the station.

The Fourth International Leprosy Conference will be held in Cairo, beginning on March 21, 1938. This conference is being organized by the International Leprosy Association, and this will be the first International Conference to be arranged by this Association since its inauguration in 1931. Three previous conferences of this nature have been held—at Berlin in 1897, at Bergen in 1909, and at Strassbourg in 1923.

The Egyptian Government is inviting all countries concerned to send official delegates. In addition to these, doctors and others interested in the subject are invited to be present. Full information can be obtained from the Secretary of the International Leprosy Association, 131 Baker Street, London, W.1.

Book Reviews

Rose and Carless' Manual of Surgery for Students and Practitioners. C. P. G. Wakeley, D.Sc. F.R.C.S., F.R.S. and J. B. Hunter, M.C., F.R.C.S. 15th ed., 2 vols., illustrated, $9.00 the set. Macmillan, Toronto, 1937.

In the fifteenth edition of this well known textbook the new editors have thoroughly revised the work, and teachers of surgery will, in the main, be satisfied if "Rose and Carless" be chosen by their students.

Chapters on the surgery of the chest and of the sympathetic nervous system have been added, and certain other chapters have been rewritten. The subjects of bacteriology, inflammation and immunity have been brought up to date. Revision of the section on appendicitis has not been so fortunately handled. The authors have evidently missed the point in Wilkie's articles on obstructive appendicitis, although they refer to them briefly. They still preach a heresy that "catarrhal appendicitis" with a fever of 101° F. and a leucocyte count of 20,000 may safely be watched for forty-eight hours in the hope of subsidence. This may be approved by some teachers of surgery but by very few in this country.

The reviewer has noticed the word "morphia" recurring many times throughout the book. This spelling is an anachronism and the authors know, or should know, that for forty years the British Pharmacopœia has disowned the "ia" ending in the names of alkaloids. The correct Latin ending of all of these is "ina" and the English "ine".

The new Rose and Carless compares well with other texts of similar purpose. In style, typography and binding it is in a class by itself.

Tweedy's Practical Obstetrics. Revised by B. Solomons, M.D., Sc.D., F.R.C.P.I. and N. M. Falkiner, M.D., Sc.D., F.R.C.P.I., Dublin. 7th ed., 773 pp., illustrated, $7.50. McAinsh, Toronto, 1937.

This edition of Tweedy's well known book carries on the plain and direct method of the first author, though the content has been largely changed. Professor Gatenby contributes a useful chapter on General Embryology. Under the conduct of normal labour attention is called to the dangers of chloroform. In the third stage control of the fundus is considered unnecessary. Early rising in the puerperium is not recommended. In the chapter on Toxæmias of Pregnancy the views of the Dublin School on the rôle played by food toxins are set forth. Reference is made to Theobald's theory of pregnancy toxæmia being a deficiency disease. In eclampsia the treatment advised is the administration of morphine, gastric and colon lavage, poultices to the loins, administration of fluid, and venesection in cases with persistently high blood pressure. The view of Irving that the occurrence of arterial spasm can explain all the pathological changes in eclampsia is accepted. In discussing hydatidiform mole and chorionepithelioma no mention is made of the value of the Aschheim-Zondek or Friedman tests after the removal or expulsion of a mole.

In a word the book lives up to its name, and the general practitioner will find it a reliable guide in the obstetrical emergencies which so often arise unexpectedly. The style is simple and direct, and therefore the advice given is likely to be retained in the memory of the reader, ready to be turned to good account when the occasion arises.

Manual of the Diseases of the Eye. C. H. May, M.D. 15th ed., revised, 498 pp., illustrated, $4.00. William Wood, Baltimore, 1937.

This book, a true "manual", for it can easily be held in the hand, has met with remarkable success, as its history shows. Since 1900 it has passed through fifteen editions, with many reprintings, and has been translated into Spanish, French, Italian, Dutch, German, Chinese and Japanese. To date, more than a quarter of a million copies have been sold. Surely, a record!

Since the first the author has had constantly in mind the thought of presenting a concise, practical and systematic book suitable for the student and general practitioner of medicine. The work is not intended as a substitute for the larger textbook, but merely as a sound foundation on which to rear a superstructure of additional knowledge, when so desired, by reference to the more elaborate books on the subject. The present edition has been carefully and thoroughly revised. The chapters on The Ophthalmoscope and on The Ocular Manifestations of General Diseases have been rewritten. Considerable change has been made in the pages relating to operations on the lids and for detachment of the retina. Obsolete matter has been eliminated and new topics have been introduced, such as, dinitrophenol cataract, inclusion bodies, inclusion blenorrhœa, treatment with acetylcholine, "floaters", gonioscopy, pontocaine, recumbent spectacles, polaroid glass, etc. It can thus be seen that the book has been brought thoroughly up to date. It continues, therefore, to fulfil its purpose admirably within its range.

Malaria in Europe. L. W. Hackett, M.D., D.P.H. 336 pp., illustrated, $3.25. McAinsh, Toronto, 1937.

This book is more comprehensive than the title indicates. The necessity for this is elaborated by the author in several of the chapters. In these he clearly shows that an understanding of conditions responsible for endemic and epidemic malaria is impossible without extensive surveys of the factors concerned in all affected areas.

In the introduction attention is drawn in a general way to the "ambiguous rôle which malaria has played through the ages". By some it has been considered to be the cause of social depression, by others the effect. Many observers view it as a parasitism capable of taking advantage of local conditions which affect the carrier, the parasite, and the human host. "Nature is as much concerned with the parasite and the mosquito as with man". The author reviews the complexity of the problem in several chapters, and in the last three discusses methods involved in control of the disease.

The following are some of the studies reviewed which have emphasized the complexity of the problem and have led to a broader understanding of condi-

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tions which seem to vary so greatly in different places: (1) the outbreaks in various parts of Europe which followed the return of infested soldiers after 1918; (2) observations on various types of anophelines, with reference to their habits, adaptability, and differentiation; (3) further investigations on the various parasites themselves; (4) the reasons for anophelism without malaria; (5) knowledge obtained about malaria in patients in whom it has been produced for therapeutic purposes; (6) the factors concerned in limiting the more serious grades of disability in endemic areas.

Conclusions reached are that malaria results from a complex factor 'X' acting in conjunction with anophelines, parasite, and man. In the various chapters this subject is to some extent dissociated into components largely from the individual and his environment. In districts from which malaria has disappeared this seems to have been due to elimination of local carrying strains of anophelines and their substitution by others, to treatment, and to elimination of reservoirs.

After indicating methods of studying affected areas, the author outlines the chief methods for reducing the frequency and severity of outbreaks.

As a study of epidemiology in general and of malaria in particular this work may be highly commended.

Charterhouse Rheumatism Clinic Original Papers. Vol. 1, 203 pp., illustrated, $4.50. McAinsh, Toronto, 1937.

This book consists of three separate papers by H. Warren Crowe and his co-workers. In Crowe's paper, "Pathogen Selective Culture and Its Bearing on the Classification and Etiology of Chronic Rheumatic Disease", all the patients studied are divided into ten groups. In outlining his methods of culturing various "foci", the author obtains a higher percentage of *S. hæmolyticus* from patients with osteo-arthritis than from those with rheumatoid arthritis, and incidentally implies an infectious basis for osteo-arthritis. These findings, and the method of classification, are not in agreement with the majority of workers in this subject, and consequently require further confirmation before acceptance.

In the second paper, H. Coke presents a "Differential Sedimentation Test". Complete details are given concerning the intricate technique and theory of the test, which necessitates a knowledge of the principles of physiological and colloidal chemistry, and especially those dealing with vanadium and its salts. The test implies again that osteo-arthritis is intimately related to infectious foci, and also that there are two subgroups, *viz.*: (*a*) "active infective", and (*b*) "chronic toxic osteo-arthritis". Furthermore "spondylitis adolescens" is subdivided into three stages. The test is considered of importance in regulating the dosage of vaccine that is used in treatment. Little is said of the other types of arthritis.

The third paper by S. Gilbert Scott, "Spondylitis Adolescens", refers to the condition known generally as Strümpell-Marie or ankylosing spondylitis ("poker-back"). The author claims that ". . . wandering rheumatic pains" between the ages of 12 and 18 constitute a "pre-spondylitic syndrome", but no mention is made of other types of rheumatic disease. He rightfully stresses the early bilateral involvement of the sacro-iliac joints, "sacro-ilitis"; and considers that these joints may act as definite "foci", preceding the calcification of the spinal ligaments. He states that decalcification of the vertebræ does not occur in these cases; and also that osteo-arthritic (hypertrophic) changes never occur in the sacroiliac joints. The necessity of early recognition and treatment is emphasized by the author, but the only methods of treatment he presents are x-ray radiation and vaccine. It must be pointed out, however, that most investigators consider this type of spondylitis to be related closely to rheumatoid arthritis, that it occurs chiefly *after* the age of twenty, and that the majority of cases do show definite decalcification of the vertebral bodies. Further, other methods of treatment are frequently advisable, which yield satisfactory results.

All things considered, the contents of this volume are essentially experimental in character. While it is obviously not a book for the practitioner, it may prove a stimulus to the research student in the realm of rheumatic diseases.

Clinical Allergy. A. H. Rowe, M.S., M.D. Sixth edition, 812 pp., $8.50. Lea & Febiger, Philadelphia, 1937.

The subject of allergy is well reviewed and discussed in this book. Little new has been added to our knowledge of the mechanism through which asthma and allied conditions are brought about, but probably Dr. Rowe is right in feeling that greater emphasis should be laid on the part played by allergy, and that it should be more constantly in the mind of the internist. It is in the developing of this point of view that he adds his quota of experience. Dr. Rowe dwells at great length on the value of his "elimination" diets, which he was the first to introduce. He points out, rightly, that valuable as skin tests are they may entirely fail to uncover a sensitization. The careful use of the elimination diets may in such cases give the key to the offending food. One is disposed to question whether the effects of these diets on some of the rather vague gastro-intestinal symptoms such as heartburn, etc., are as specific and permanent as this book would lead us to suppose. It is possible that careful dieting helps in a non-specific way. This is not to say that gastro-intestinal symptoms may not be due to specific foods. Of course they may. One meets with many cases, however, in which no improvement of allergic disorders is obtained even when a specific sensitivity is discovered and treated.

The book is well worth having as a source of information on the multitude of sensitivities which man may develop.

Latent Syphilis and the Autonomic Nervous System. G. Evans, M.A., D.M., F.R.C.S., D.O.M.S. 2nd ed., 158 pp., illustrated, $2.25. Macmillan, Toronto, 1937.

This is a somewhat unusual book. The author is a general practitioner who has practised for many years in a small Welsh seaport town where syphilis is evidently prevalent, and has combined a careful study of his patients with an intimate knowledge of their previous history and of their family background. From such a personal study, supported by an adequate knowledge of the literature, he is convinced that latent syphilis is being constantly overlooked; the Wassermann reaction, admittedly negative in a large percentage of the cases of aortitis and tabes dorsalis, was absent in more than 50 per cent of the cases of latent syphilis particularly considered in this book.

The syphilitic virus passes almost at once into the lymphatic system, including the thoracic and abdominal lymphatic glands; in close proximity to these glands lie the main sympathetic ganglia whose involvement from the virus has been, according to the author, overlooked, though the spread of syphilis from the thoracic glands along the lymphatics to the aorta and to the nervous system is admitted by all. From such involvement of the autonomic nervous system many cases of asthma, vasomotor disturbances in the extremities, so-called nervous dyspepsia, and obscure abdominal pain, arise. Thus, baldly stated, the main thesis is apt to be discredited offhand, but the surprisingly intimate family and personal histories, combined with the associated symptoms of the indi-

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vidual patients, make out, on close reading, a much better case than might at first be expected, and the improvement or cure under bismuth, mercury and iodide lends support to the author's views. Pathological conditions of the tongue form an interesting and instructive chapter. The author believes also that syphilis is a common pre-cancerous state.

The book is written in an easy style and is worth close study, as admittedly syphilis is often overlooked; an uncritical acceptance of many of its views is obviously impossible.

Clinical Endocrinology. S. A. Loewenberg. 825 pp., illustrated, $8.00. Davis, Philadelphia, 1937.

This book will be widely welcomed. Not only has this fascinating subject been thoroughly reviewed but a great deal of information has been added from the author's large experience in the finest hospitals of Philadelphia. Case reports of practically every disease presented here have been personally observed and studied. Like an able teacher he presents the subject in a clear, orderly manner, simple enough for the medical student to grasp a clear idea of the subject on hand.

The historical discussion of endocrinology opens the first chapter. Following are chapters on anatomy and physiology. Then diseases associated with separate clinics or group of clinics are systematically treated, and the work closes with a comprehensive discussion of laboratory interpretation. The book is up to date, modern in every respect, and well illustrated.

Fundamentals of Bacteriology. M. Frobisher, Jr., B.S., D.Sc., F.A.A.S., Associate in Bacteriology, Johns Hopkins University. 474 pp., illustrated, $3.75. McAinsh, Toronto, 1937.

The object of this book is to provide a cultural and philosophical background for any educated reader so that an appreciation may be obtained of bacteria, not merely as parasites and of exclusive medical interest but as microscopic plants of much wider importance, with interesting and valuable synthetic and analytic powers. Rather detailed accounts are given of a relatively few representative bacterial phenomena rather than a superficial survey of a great many. Bacteria of the soil, water, dairy, iron, slime and many other types are considered with the industrial and other applications stressed, but without overlooking the broad biological significance of bacterial life. The bacteria producing disease in plants, animals and man are revealed clearly, dramatically and discriminatingly. The illustrations are excellent and the most interesting and important points are given sufficient attention to stimulate almost anyone. This book can be recommended to all those to whom general biology appeals, and the reader has the satisfaction of knowing that the writer speaks with authority. Two chapters on the histological aspects and the influences on natural philosophy brought about by the discovery of bacteria are particularly well done.

A Textbook of Medical Bacteriology. R. W. Fairbrother, D.Sc., M.D., M.R.C.P. 437 pp., illustrated, $4.50. Macmillan, Toronto, 1937.

This book is an outline of the medical aspects of bacteriology. It is especially written for the medical student, to direct his attention to those branches of the subject that are of medical importance. The book is divided into three parts: General Bacteriology; Systematic Bacteriology and General Technique. Each chapter is well written, much theory and technical detail advantageously eliminated, and the most important branches of bacteriology ably presented. The application of bacteriological methods in prevention, diagnosis and treatment of disease, as given in this volume, should be of great assistance to the medical student as well as to the clinician.

Handbook of Orthopædic Surgery. A. R. Shands, Jr., B.A., M.D., Associate Professor of Surgery, Duke University School of Medicine and R. B. Raney, B.A., M.D. 510 pages, illustrated, $6.00. McAinsh, Toronto, 1937.

This book has been written for the medical student and general practitioner to present the fundamental facts and principles of orthopædic surgery. It is admirably suited to this purpose. It is written in goodly form of presentation of each disease process which makes for vivid portrayal. The paper is excellent and the print of fairly large size. It is up to date in scientific concept. The positiveness expressed in the discussion of treatment should be of help.

Treatment in Psychiatry. O. Diethelm, M.D., New York. 470 pp., $4.00. Macmillan, New York, 1936.

Of all the treatment procedures in the field of medicine psychiatric treatment is perhaps the most difficult because the results depend to such a large extent on meeting the needs of the individual patient as well as upon the personal relationship which is established between the physician and the patient. A clear statement, therefore, of the principles involved in psychiatric treatment and the manner in which it can best be applied is very welcome indeed.

In this book Dr. Diethelm summarizes very adequately the present-day approach to the treatment of personality disorders and mental disease. He includes a discussion of the approach to problems in personality maladjustment which do not manifest themselves in the form of definite mental disease. The treatment of such conditions as stuttering, tics, social maladjustment and sexual difficulties is presented in such an understandable manner that the average physician can get a great deal of insight into the best method of approaching these difficulties. The question of psychosomatic relationships, which in recent years has assumed increasing importance, is very adequately presented, with a clear indication of the so-called psychological approach to these conditions. Throughout the book the author takes great pains to discuss treatment in detail, with particular reference to the manner in which the physician who has not been specially trained in psychiatry can be of help to his patient by keeping in mind certain fundamental principles of psychiatric treatment. Numerous case histories illustrate the text and help to make this book a valuable addition to recent psychiatric literature.

Children Handicapped by Cerebral Palsy. E. E. Lord, Ph.D. 105 pp., $1.25. Commonwealth Fund, New York, 1937.

The author has presented in this small publication a very valuable contribution to the management and training of children handicapped by cerebral paralysis. The problem and the training of the handicapped child are approached from several angles. The fundamental need of muscular relaxation is emphasized in beginning any course of training, and attention is called to the fact that active movements must be designed to appear of value to the patient, in order that interest may be retained in what would otherwise be a very monotonous procedure. Any course of training must commence early in the child's life if motor improvement is to be expected. In discussing the limitations of the ordinary intelligence tests one need not be particularly concerned with the mental age, for marked discrepancies may be found to exist between intelligence ratings and educability. If a testing program is to have any particular value it must bring out the variations in achievement.

This publication is based largely, on personal observation and contains many practical suggestions. Such a book will be found of value to both physicians and physiotherapists who may be engaged in treating such handicapped children.

Physiology in Health and Disease. C. J. Wiggers, M.D. 2nd ed., 1124 pp., illustrated., $9.00. Lea & Febiger, Philadelphia, 1937.

In this edition an excellent attempt has been made to bring the first edition up to date. The entire book has been revised and chapters have been added to include and elucidate some of the newer researches in pure and applied physiology. This is particularly made manifest in the chapters on bio-energetics and hormonal inter-relationships. Probably the most useful contribution in this new edition is the analysis of clinical conditions from the point of view of disturbed function, and, while there are several isolated statements that one may not agree with, the whole material is ably handled. This is particularly true in the chapters dealing with renal diseases.

It is the feeling of the reviewer that we are fast approaching a time when clearer bounds must be set by authors to the realms of what is physiology and what must be considered biochemistry. The present work does not err greatly in that regard, but it is felt that its usefulness would be improved if the purely biochemical considerations were deleted.

The entire work, despite its size, gives a clear, concise account of the subjects dealt with. It is very readable, amply illustrated, extremely well indexed, and the bibliographies well selected and up to the minute. It may be highly recommended to students and practitioners alike.

The Metabolism of Living Tissues. E. Holmes, M.A., M.D. 235 pages, $2.25. Macmillan, Toronto, 1937.

This little book of 235 pages is one of a series of small monographs published by the Cambridge University Press. Two others have already appeared, dealing with different aspects of biochemistry.

It is a remarkably good treatment of the modern outlook on tissue metabolism. In the introductory chapter current views of protein structure, orientation of molecules in surface films, the possible relation of these to enzyme action, and the embodiment of these views in theories of cellular reactions are discussed in a simple, clear but stimulating manner. There are fourteen chapters dealing with such topics as Enzymes, Oxidations, the Nitrogen, Carbohydrate and Fat Metabolism of the liver, the Hormones, the Vitamins, etc. The discussions of biological oxidations and of the chemistry of muscular contraction are specially good. While the author does not attempt to discuss details of reactions, his exposition of the chemical aspects of the dynamics of living matter and his tentative explanations of obscure phenomena are the most inspiring that the reviewer has read in recent years. It is a book which should be studied by all students of the biological as well as of the medical sciences.

Clinical Laboratory Diagnosis. S. A. Levinson, M.S., M.D. 877 pp., illustrated, $9.50. Lea & Febiger, Philadelphia, 1937.

This publication is a fine example of how much can be compressed into a handy volume without sacrificing subject matter or clarity. Its purpose is to give the student, intern, practising physician and technician a review of clinical laboratory diagnosis to meet their needs, and the authors have undoubtedly achieved their purpose. It is unique in its presentation, including the unusual feature in books of this type of special chapters on laboratory procedures in Pædiatrics and in Legal Medicine. Worthy of note also are the very brief reviews of Anatomy, Biochemistry and Physiology which precede the more important chapters. The chapter on Hæmatology is exceptionally well treated. The procedures for the usual laboratory routine are very instructively presented and at a glance one becomes familiar with the subject. This book, profusely illustrated and with many excellent charts, ends with an appendix "outlining the lectures and laboratory procedures, presented in the course of Clinical Pathology at the University of Illinois, College of Medicine". This is an outstanding work and may be highly recommended.

Laboratory Outline in Filterable Viruses. R. R. Hyde, Johns Hopkins University. 85 pp., $1.50. Macmillan, Toronto, 1937.

The virus diseases have been attracting so much attention, and such a rapid accumulation of new technical methods has occurred in recent years that this short outline of two courses given to graduate students in the authors' laboratories is particularly seasonable. The first course deals with the nature and behaviour of the filterable viruses, and the second with the histo-pathology of certain virus diseases. Anyone wishing to understand the mode of approach to a study of viruses will find this guide invaluable, and since it is written by one of our greatest authorities in this field it can be read with a feeling that it is no mere compilation but rather the reasoned outlook of a very original thinker. The problems of filters and ultra-filtration are rather fully considered; experiments with bacteriophage and with representatives of viruses affecting birds, animals and man; the cultivation of the viruses; the study of inclusion-bodies and other phases of the subject are all arranged for practical study, so that even reading these outlines is an education in the field of viruses.

Histological Technique. A. A. Krajian. 217 pp. McAinsh, Toronto, 1936.

This is a practical handbook which describes in compact form many improved methods for the preparation of material for microscopic examination. It also contains a wide selection of well known standard methods which have proved so useful in histological investigations.

The various steps in each method are outlined in such a manner that it makes it easy to follow the instructions. The author highly recommends the use of frozen sections as a routine method in pathological investigations. Gum dammar is preferred to Canada balsam. Colophonium is used for Wright's blood stain. Formalin-fixed tissues are deformalinized, when necessary, in a weak solution of ammonia. Unfortunately, in all formulæ the author has decided to use the name of the gas (formaldehyde) when in fact its 40 per cent aqueous solution (formalin) is what is required.

Considerable space is devoted to methods for studying the nervous system. The author describes his own method for staining myelin sheaths, which can be completed in only one hour. He describes combined stains for reticulum and collagen fibres and for elastic and collagen fibres. Methods are described for staining, bacteria, pigments, and special organic and inorganic substances in tissues. The final chapter includes a lot of miscellaneous information including the fixing and preservation of museum specimens.

In the field of histological investigations, improved methods of technique are always welcome, and we are indebted to the author for the valuable contributions contained in his book.

BOOKS RECEIVED

Principles of Medical Statistics. A. Bradford Hill, D.Sc., Ph.D., Reader in Epidemiology and Vital Statistics, University of London. 171 pages, 6s. net. The Lancet, Ltd., London, 1937.

The Practice of Ionization. J. Newton Dyson, M.R.C.S., L.R.C.P. 178 pages, $1.50. Henry Kimpton, London, 1937.

Ten Million Americans Have It. S. W. Becker, M.D., Associate Professor of Dermatology and Syphilology, University of Chicago. 220 pages, $1.75. J. B. Lippincott, Phila., London and Montreal, 1937.